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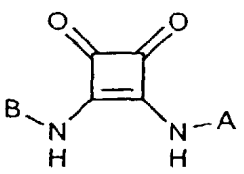
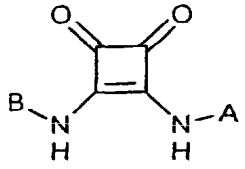
(54) Title: 3,4-DI-SUBSTITUTED CYCLOBUTENE-1, 2-DIONES AS CXC-CHEMOKINE RECEPTOR LIGANDS



(I)



(II)

(57) Abstract: Disclosed are novel compounds of the formula (I)or a pharmaceutically acceptable salt or solvate thereof. Also disclosed is the treatment of chemokine-mediated diseases using compounds of the formula (II)

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3,4-DI-SUBSTITUTED CYCLOBUTENE-1,2-DIONES AS CXC-CHEMOKINE RECEPTOR LIGANDS

FIELD OF THE INVENTION

The present invention relates to novel substituted cyclobutenedione compounds, pharmaceutical compositions containing the compounds, and the use of the compounds and formulations in treating CXC chemokine-mediated diseases.

BACKGROUND OF THE INVENTION

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T-cells, eosinophils, basophils, neutrophils and endothelial cells to sites of inflammation and tumor growth. There are two main classes of chemokines, the CXC-chemokines and the CC- chemokines. The class depends on whether the first two cysteines are separated by a single amino acid (CXC-chemokines) or are adjacent (CC-chemokines). The CXC-chemokines include interleukin-8 (IL-8), neutrophil-activating protein-1 (NAP-1), neutrophil-activating protein-2 (NAP-2), GROα, GROβ, GROγ, ENA-78, GCP-2, IP-10, MIG and PF4. CC chemokines include RANTES, MIP -1α, MIP-2β, monocyte chemotactic protein-1 (MCP-1), MCP-2, MCP-3 and eotaxin. Individual members of the chemokine families are known to be bound by at least one chemokine receptor, with CXC-chemokines generally bound by members of the CXCR class of receptors, and CC-chemokines by members of the CCR class of receptors. For example, IL-8 is bound by the CXCR-1 and CXCR-2 receptors.

Since CXC-chemokines promote the accumulation and activation of neutrophils, these chemokines have been implicated in a wide range of acute and chronic inflammatory disorders including psoriasis and rheumatoid arthritis. Baggiolini et al., FEBS Lett. 307, 97 (1992); Miller et al., Crit. Rev. Immunol. 12, 17 (1992); Oppenheim et al., Annu. Fev. Immunol. 9, 617 (1991); Seitz et al., J. Clin. Invest. 87, 463 (1991); Miller et al., Am. Rev. Respir. Dis. 146, 427 (1992); Donnely et al., Lancet 341, 643 (1993).

ELRCXC chemokines including IL-8, GROα, GROβ, GROγ, NAP-2, and ENA-78 (Strieter et al. 1995 JBC 270 p. 27348-57) have also been implicated in the induction of tumor angiogenesis (new blood vessel growth). All of these chemokines are believed to exert their actions by binding to the 7 transmembrane G-protein coupled receptor CXCR2 (also known as IL-8RB), while IL-8 also binds CXCR1 (also known as IL-8RA). Thus, their angiogenic activity is due to their binding to and activation of CXCR2, and possible CXCR1 for IL-8, expressed on the surface of vascular endothelial cells (ECs) in surrounding vessels.

Many different types of tumors have been shown to produce ELRCXC chemokines and their production has been correlated with a more aggressive phenotype (Inoue et al. 2000 Clin Cancer Res 6 p. 2104-2119) and poor prognosis (Yoneda et. al. 1998 J Nat Cancer Inst 90 p. 447-454). Chemokines are potent chemotactic factors and the ELRCXC chemokines have been shown to induce EC chemotaxis. Thus, these chemokines probably induce chemotaxis of endothelial cells toward their site of production in the tumor. This may be a critical step in the induction of angiogenesis by the tumor. Inhibitors of CXCR2 or dual inhibitors of CXCR2 and CXCR1 will inhibit the angiogenic activity of the ELRCXC chemokines and therefore block the growth of the tumor. This anti-tumor activity has been demonstrated for antibodies to IL-8 (Arenberg et al. 1996 J Clin Invest 97 p. 2792-2802), ENA-78 (Arenberg et al. 1998 J Clin Invest 102 p. 465-72), and GROα (Haghnegahdar et al. J. Leukoc Biology 2000 67 p. 53-62).

Many tumor cells have also been shown to express CXCR2 and thus tumor cells may also stimulate their own growth when they secrete ELRCXC chemokines. Thus, along with decreasing angiogenesis, inhibitors of CXCR2 may directly inhibit the growth of tumor cells.

Hence, the CXC-chemokine receptors represent promising targets for the development of novel anti-inflammatory and anti-tumor agents.

There remains a need for compounds that are capable of modulating activity at CXC-chemokine receptors. For example, conditions associated with an increase in IL-8 production (which is responsible for chemotaxis of neutrophil and T-cell subsets into the inflammatory site and growth of tumors) would benefit by compounds that are inhibitors of IL-8 receptor binding.

SUMMARY OF THE INVENTION

This invention provides a method of treating a chemokine mediated disease in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one compound (e.g., 1-3, and usually one) of formula IA (or a pharmaceutically acceptable salt or solvate thereof), as described below, said chemokine mediated disease being selected from the group consisting of: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

This invention provides a method of treating acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, or chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually

one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof), as described below.

This invention provides a method of treating a chemokine mediated disease in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds

This invention provides a method of treating acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, or chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds, concurrently or sequentially with: (a) a microtubule affecting agent, or (b) an antineoplastic agent, or (c) an anti-angiogenesis agent, or (d) a VEGF receptor kinase inhibitor, or (e) antibodies against the VEGF receptor, or (f) interferon, and/or g) radiation.

This invention also provides a method of inhibiting angiogenesis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization), in a patient in need of such treatment, comprising administering to said patient and effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides a method of treating a disease selected from the group consisting of: gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds.

This invention also provides novel compounds selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

This invention also provides novel compounds selected from the group consisting of the pharmaceutically acceptable salts (e.g., sodium, or calcium salts), or solvates, of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1-3, usually 1) compound selected from the compounds of formulas 1.0A,

3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds, and a pharmaceutically acceptable carrier.

This invention also provides a method of treating a chemokine mediated disease in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating cancer in a patient in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below, concurrently or sequentially with: (a) a microtubule affecting agent, or (b) an antineoplastic agent, or (c) an anti-angiogenesis agent, or (d) a VEGF receptor kinase inhibitor, or (e) antibodies against the VEGF receptor, or (f) interferon, and/or g) radiation.

This invention also provides a method of inhibiting angiogenesis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating angiogenic ocular disease (e.g., ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization), in a patient in need of such treatment, comprising administering to said patient and effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides a method of treating a disease selected from the group consisting of: gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis, in a patient in need of such treatment, comprising administering to said patient an effective amount of at least one (e.g., 1-3, usually 1) compound of formula IB, as described below.

This invention also provides novel compounds of formula IB, as described below.

This invention also provides novel compounds selected from the group consisting of the pharmaceutically acceptable salts (e.g., sodium, or calcium salts), or solvates, of the compounds of formula IB, as described below.

This invention also provides a pharmaceutical composition comprising at least one (e.g., 1-3, usually 1) compound of formula IB, as described below, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

When any variable occurs more than one time in any moiety, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless indicated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. For example, the definition of "alkyl" also applies to the "alkyl" portion of "alkoxy".

"Patient" includes both human and other mammals, preferably human.

"Mammal" includes a human being, and preferably means a human being.

"Alkyl" means a straight or branched saturated hydrocarbon chain having 1 to 20 carbon atoms, preferably 1 to 12 carbon atoms, more preferably 1 to 6 carbon atoms.

"Alkoxy" means an alkyl-O- group wherein alkyl is as defined above. Non-limiting examples of alkoxy groups include: methoxy, ethoxy, n-propoxy, iso-propoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Alkenyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon double bond, and 2 to 20 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 6 carbon atoms. Non-limiting examples of alkenyl groups include: ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means a straight or branched aliphatic hydrocarbon group having at least one carbon-carbon triple bond, and 2 to 15 carbon atoms, preferably 2 to 12 carbon atoms, and more preferably 2 to 4 carbon atoms. Non-limiting examples of

alkynyl groups include ethynyl, propynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl, and decynyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system, wherein at least one ring is aromatic, comprising about 6 to about 14 carbon atoms, and preferably about 6 to about 10 carbon atoms. Non-limiting examples of suitable aryl groups include: phenyl, naphthyl, indenyl, tetrahydronaphthyl, indanyl, anthracenyl, and fluorenyl.

"Arylalkyl" means an aryl group, as defined above, bound to an alkyl group, as defined above, wherein the alkyl group is bound to the parent moiety. Non-limiting examples of suitable arylalkyl groups include benzyl, phenethyl and naphthleneylmethyl.

"Cycloalkyl" means saturated carbocyclic rings having 3 to 10 (e.g., 3 to 7) carbon atoms, preferably 5 to 10 carbon atoms, and more preferably 5 to 7 carbon atoms, and having one to three rings. Non-limiting examples of cycloalkyl groups include: cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

"Cycloalkylalkyl" means a cycloalkyl group bound to the parent moiety through an alkyl group. Non–limiting examples include: cyclopropylmethyl and cyclohexylmethyl.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising 3 to 10 carbon atoms, and preferably 5 to 10 carbon atoms, and having at least one carbon-carbon double bond. Preferred cycloalkenyl rings have 5 to 7 carbon atoms. Non-limiting examples of cycloalkyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, and norbornenyl.

"Halo" means fluoro, chloro, bromo, or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Haloalkyl" means an alkyl group as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Heterocyclyl" or "heterocyclic" or "heterocycloalkyl" means a non-aromatic saturated monocyclic or multicyclic ring system (i.e., a saturated carbocyclic ring or ring system) comprising 3 to 10 ring atoms (e.g., 3 to 7 ring atoms), preferably 5 to 10 ring atoms, in which one or more of the atoms in the ring system is an element other

than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls have 5 to 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom, respectively, is present as a ring atom. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of monocyclic heterocyclyl rings include: piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, and tetrahydrothiopyranyl.

The term heterocyclic acidic functional group is intended to include groups such as, pyrrole, imidazole, triazole, tetrazole, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising 5 to 14 ring atoms, preferably 5 to 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain 5 to 6 ring atoms. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of heteroaryls include: pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, and benzothiazolyl.

"Heteroarylalkyl" means a heteroaryl group, as defined above, bound to an alkyl group, as defined above, where the bond to the parent moiety is through the alkyl group.

N-oxides can form on a tertiary nitrogen present in an R substituent, or on =N- in a heteroaryl ring substituent and are included in the compounds of formula I.

The term "prodrug," as used herein, represents compounds that are rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-

drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

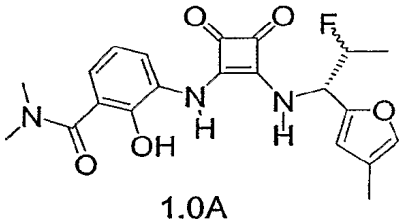
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

As used in the methods of this invention,"an effective amount" means a therapeutically acceptable amount (i.e., that amount which provides the desired therapeutic effective).

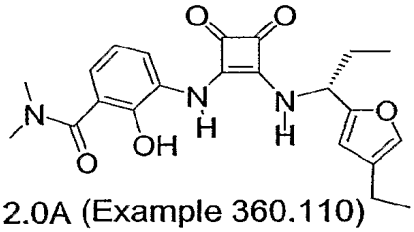
Also, as used herein, with reference to chemical structures or formulas, "Bn" represents benzyl, "Et" represents ethyl, "Me" represents methyl, and "Ph" represents phenyl.

Representative embodiments of this invention are described below. The embodiments have been numbered for purposes of reference thereto.

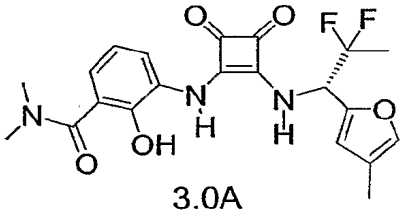
Compounds of formulas 1.0A, 2.0A, 3.0A, 4.0A, 5.0A and 6.0A are:



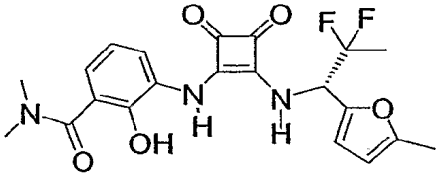
1.0A



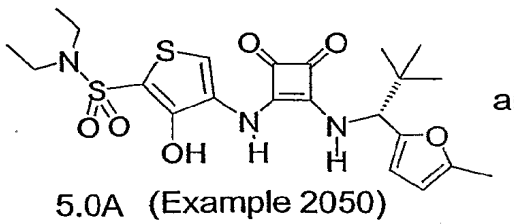
2.0A (Example 360.110)



3.0A

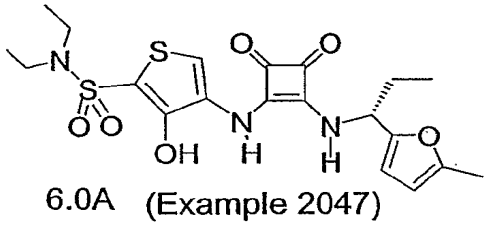


4.0A (Example 1207)



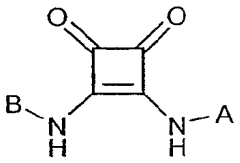
5.0A (Example 2050)

and



6.0A (Example 2047)

For the methods of treatment that use compounds of formula IA, as described above, said compounds of formula IA are:

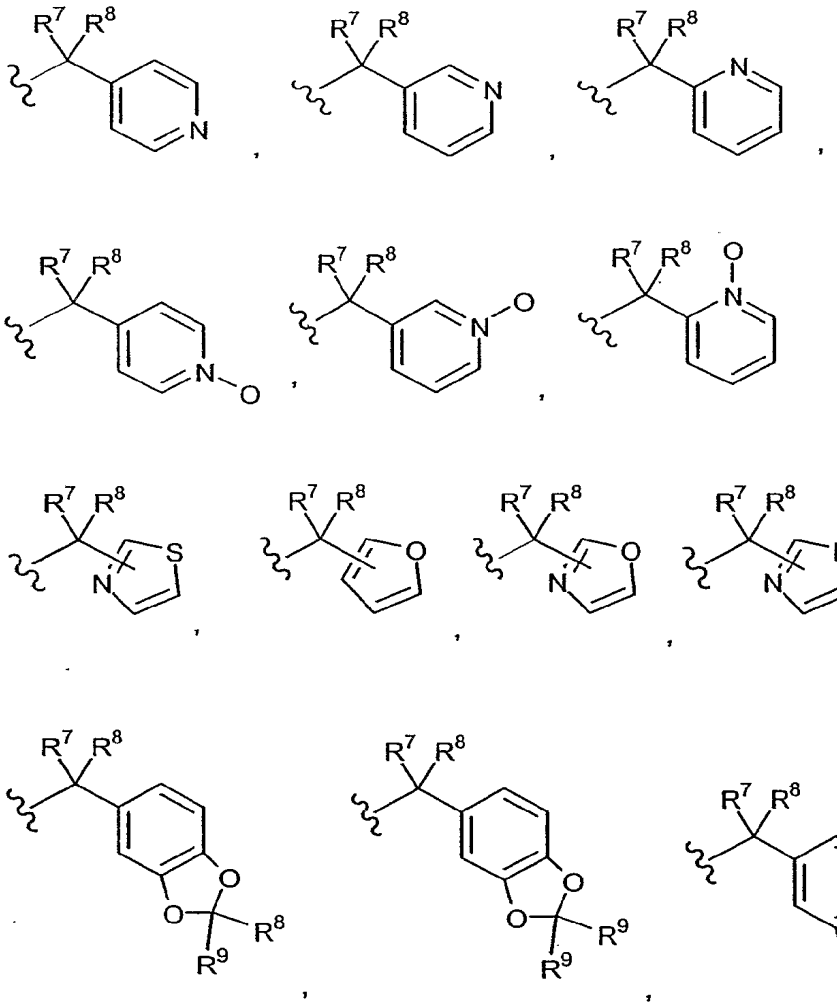


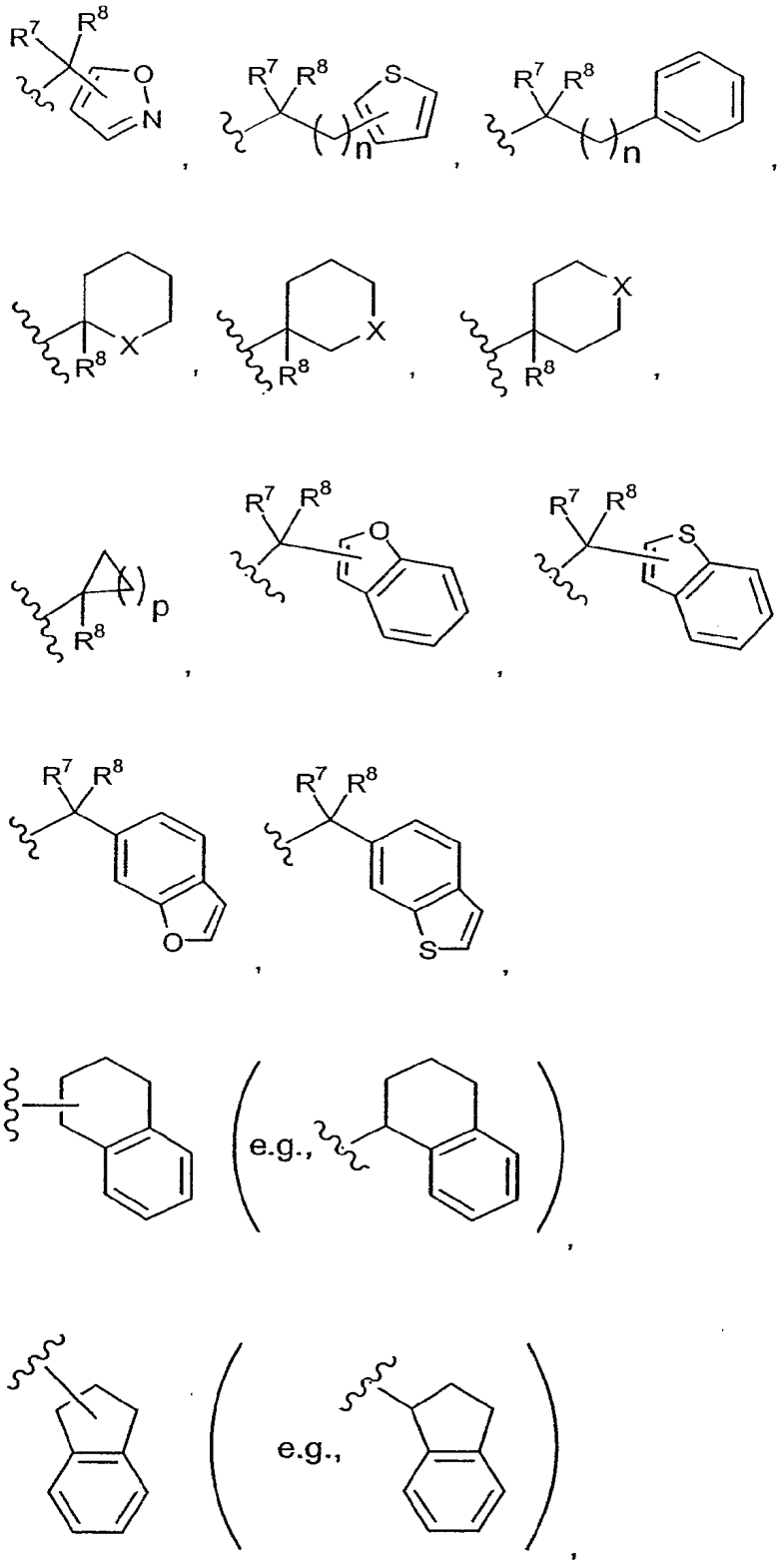
(IA)

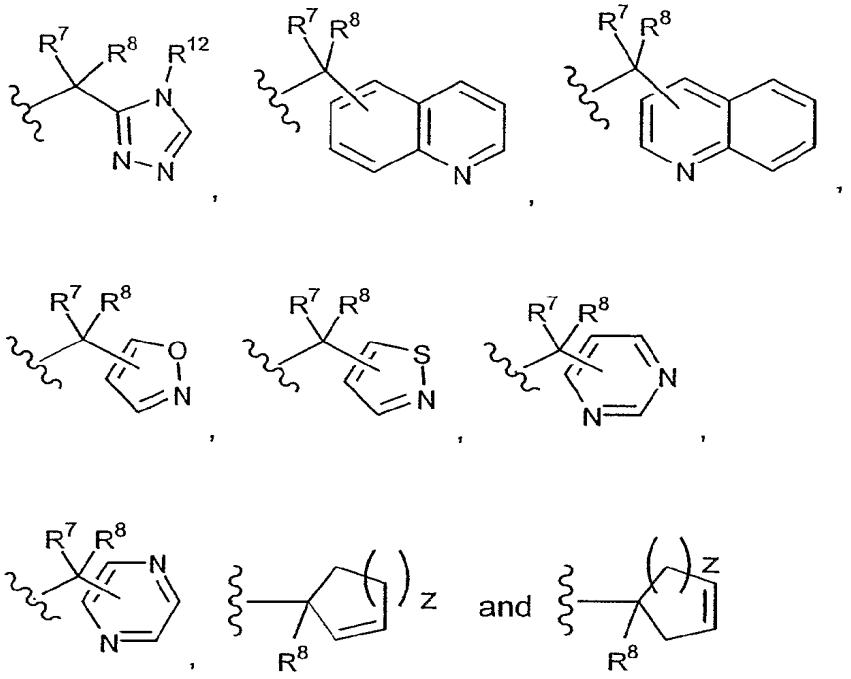
and the pharmaceutically acceptable salts (e.g., sodium or calcium salt) and solvates thereof, wherein:

A is selected from the group consisting of:

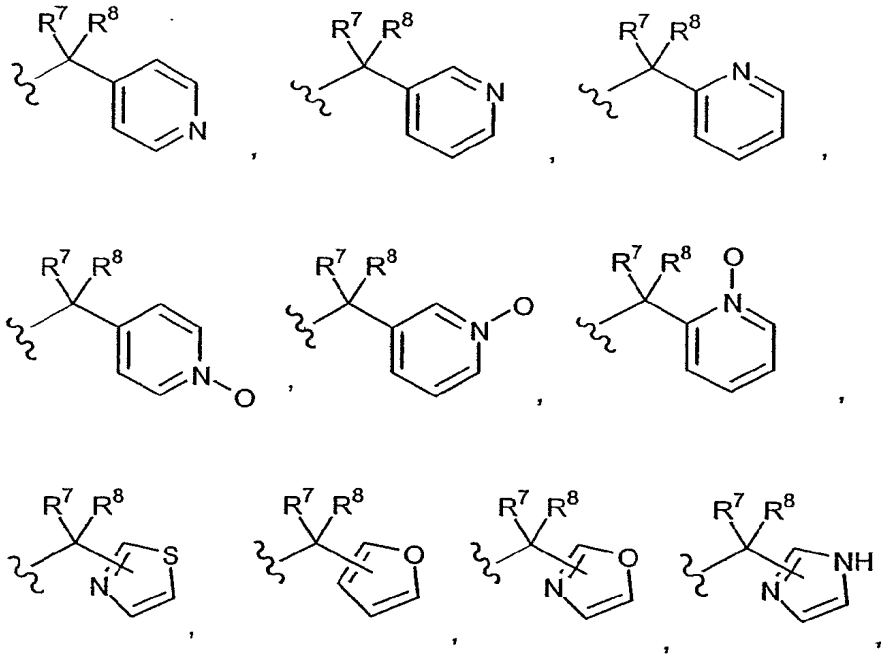
(1)

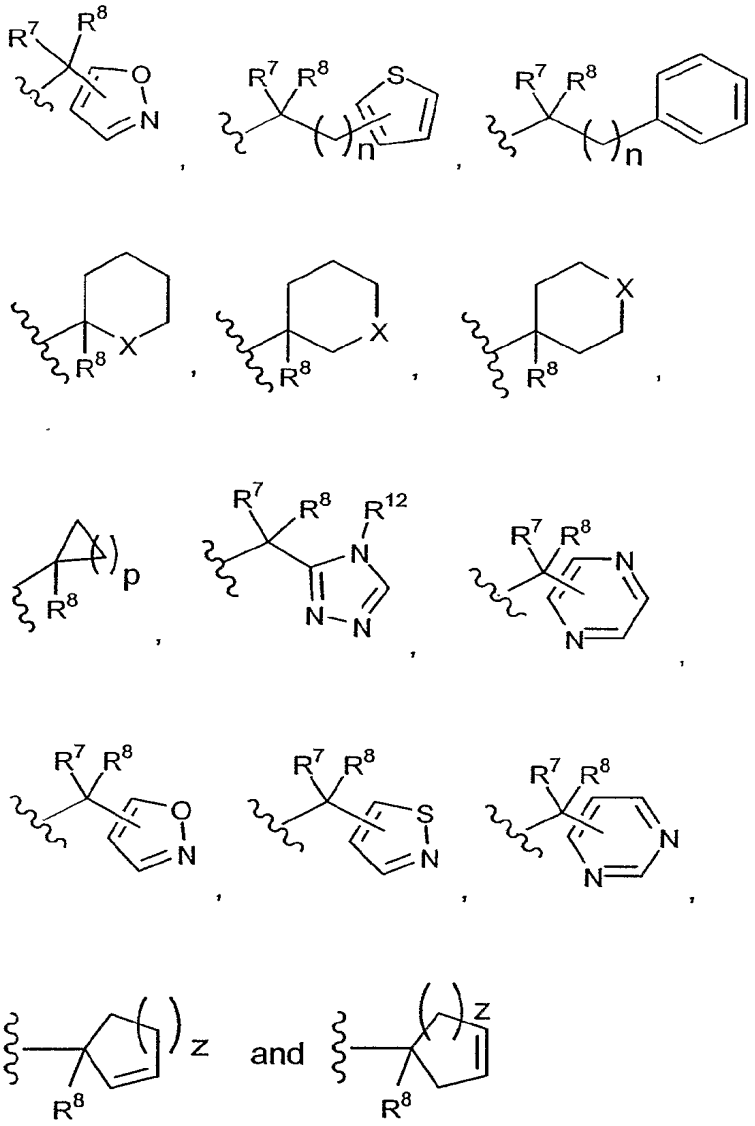



R7 R8
O
N
S
n
X
p
e.g.,
e.g.,



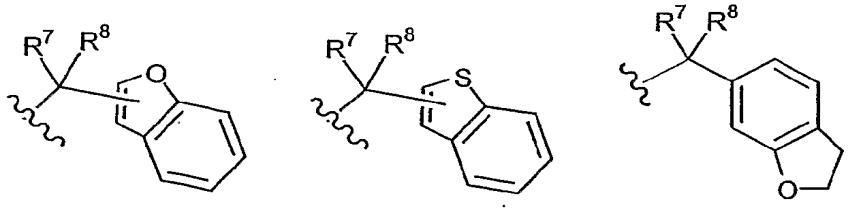
(2)

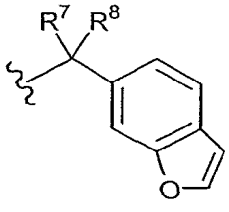
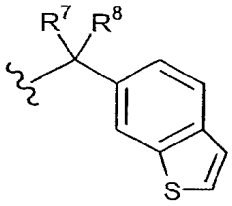
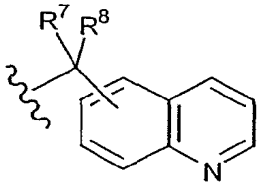
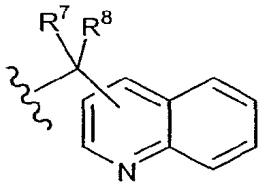
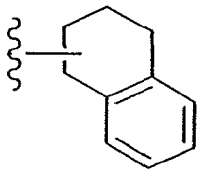
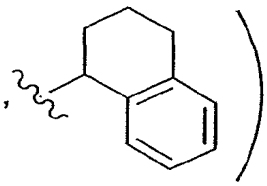




wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(3)



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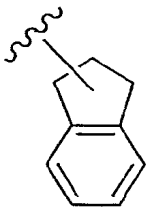
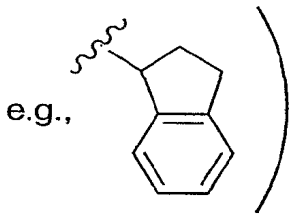
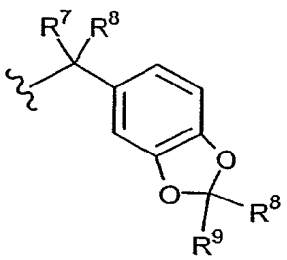



wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

(4)



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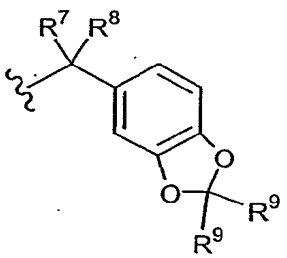
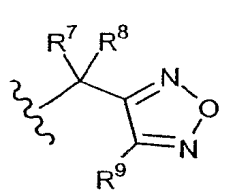


wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

(5)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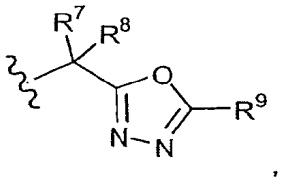
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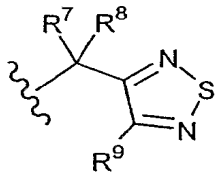
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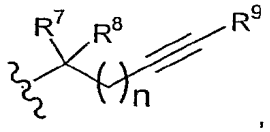
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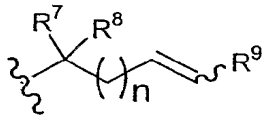
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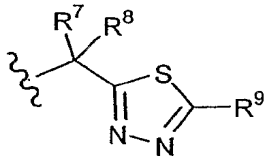
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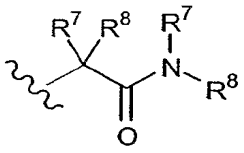
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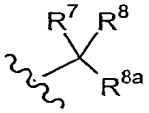
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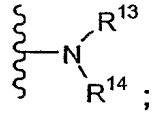
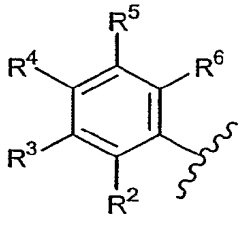

;

B is selected from the group consisting of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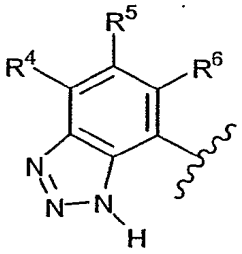
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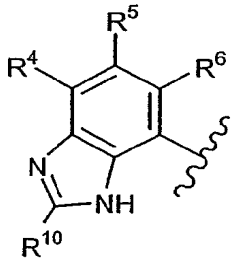
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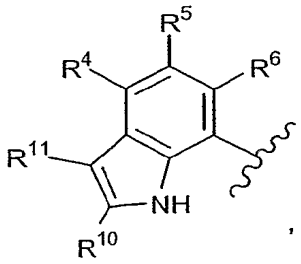
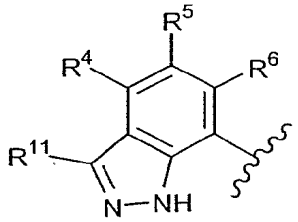
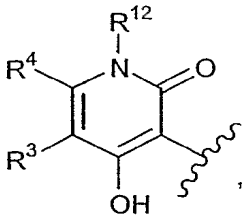
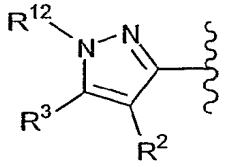
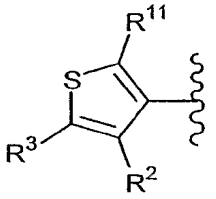
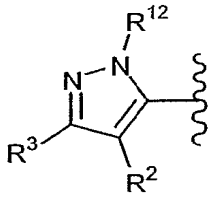
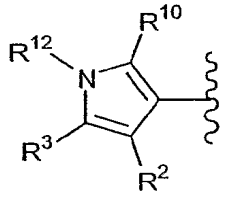
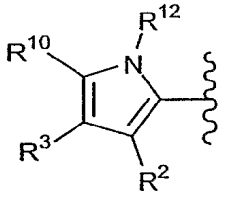
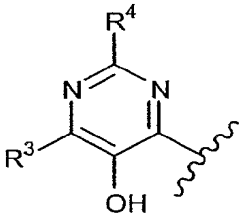
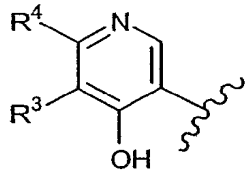
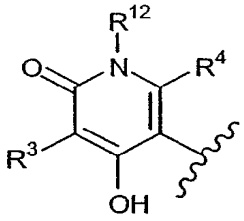
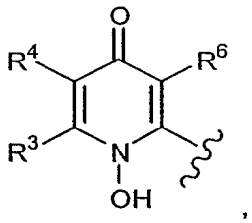
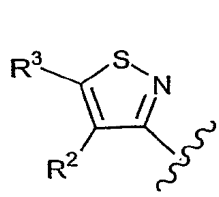
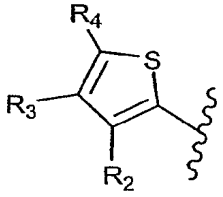
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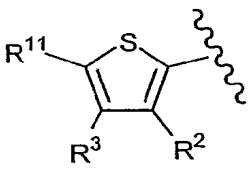

;

n is 0 to 6;

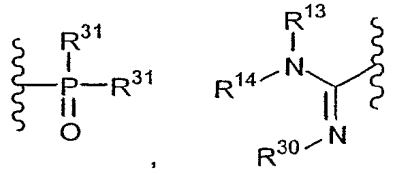
p is 1 to 5;

X is O, NH, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, - $S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,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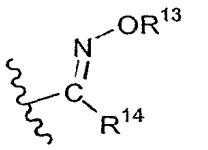
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wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or

substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more (e.g., 1 to 6) substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,
o) $-SO_2R^{13}$,
p) $-OC(O)R^{13}$,
q) $-OC(O)NR^{13}R^{14}$,
r) $-NR^{13}C(O)R^{14}$, and
s) $-NR^{13}CO_2R^{14}$;

(fluoroalkyl is one non-limiting example of an alkyl group that is substituted with halogen);

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,
b) halogen,
c) $-CF_3$,
d) $-COR^{13}$,
e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) –CN,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

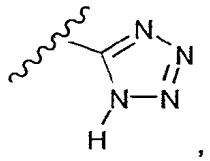
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



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p) alkyl substituted with one or more (e.g., one) –OH groups (e.g., $-(CH_2)_qOH$, wherein q is 1-6, usually 1 to 2, and preferably 1),

q) alkyl substituted with one or more (e.g., one) $-NR^{13}R^{14}$ group (e.g., $-(CH_2)_qNR^{13}R^{14}$, wherein q is 1-6, usually 1 to 2, and preferably 1), and

r) $-N(R^{13})SO_2R^{14}$ (e.g., R^{13} is H and R^{14} is alkyl, such as methyl);

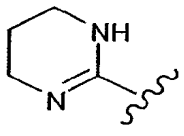
each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, hydrogen, alkyl (e.g., C_1 to C_6, such as methyl), halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or

substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl (wherein "heterocyloalkyl" means heterocyclic); wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, $-CF_3$, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, halogen, and $-NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered heterocyclic ring), said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., there is 1 to 3 substituents on the ring formed when the R^{13} and R^{14} groups are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group (i.e., a heterocyclic group that has at least one, and preferably one, double bond in a ring, e.g.,



;

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: $-SO_2$alkyl, $-SO_2$aryl, $-SO_2$cycloalkyl, and $-SO_2$heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

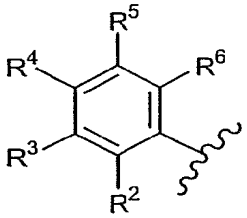
each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

t is 0, 1 or 2.

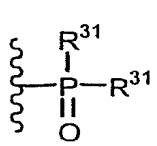
Embodiments of the methods of treatment that use compounds of formula IA, as described above, are described below. The embodiments have been numbered for purposes of reference thereto.

Embodiment No. 1 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:

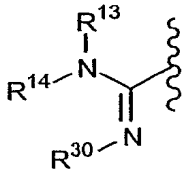
(1)



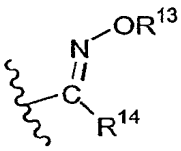
provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



,

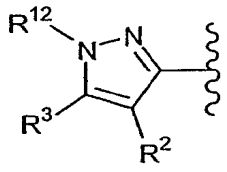


and



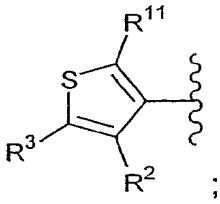
;

(2)



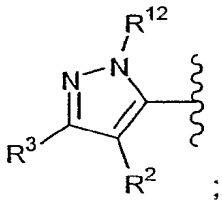
;

(3)



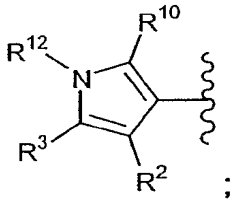
;

(4)



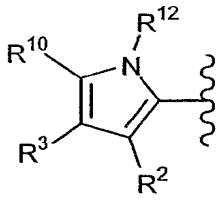
;

(5)



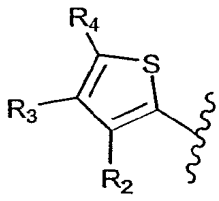
;

(6)



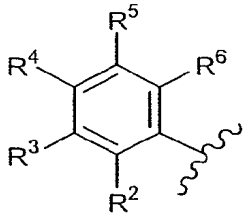
; and

(7)

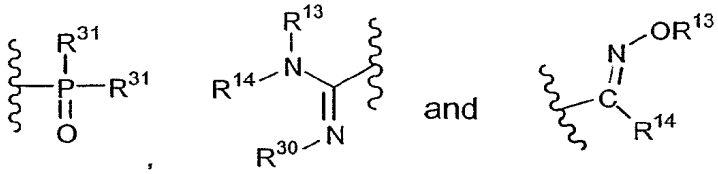


wherein all substituents are as defined for the novel compounds of formula IA.

Embodiment No. 2 is directed to the the methods of treatment that use compounds of formula IA wherein B is:

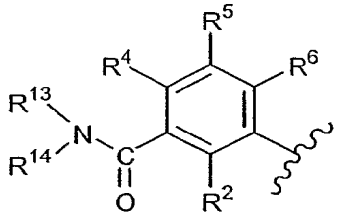


wherein R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



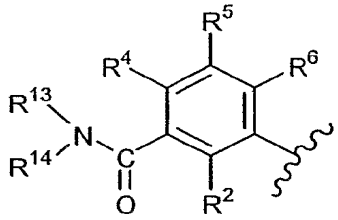
and all other substituents are as defined in formula IA.

Embodiment No. 3 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



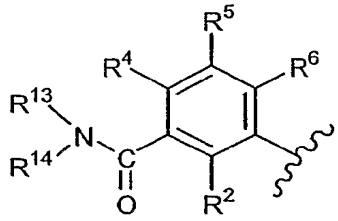
and all other substituents are as defined in formula IA.

Embodiment No. 4 is directed to the the methods of treatment that use compounds of formula IA wherein B is



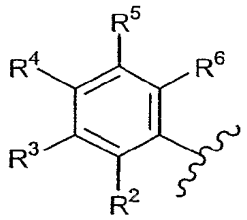
R^{13} and R^{14} are each the same or different alkyl group, and all other substituents are as defined in formula IA.

Embodiment No. 5 is directed to the the methods of treatment that use compounds of formula IA wherein B is

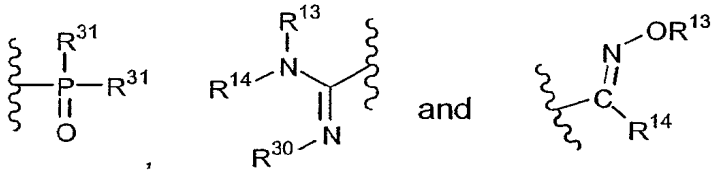


and (1) R^2 is –OH, and all other substituents are as defined in formula IA, or (2) R^2 is –OH, and R^{13} and R^{14} are each the same or different alkyl group, and all other substituents are as defined in formula IA.

Embodiment No. 6 is directed to the the methods of treatment that use compounds of formula IA wherein B is

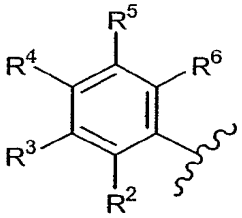


R^3 is selected from the group consisting of:

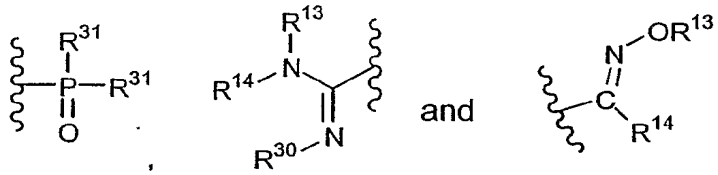


and all other substituents are as defined in formula IA.

Embodiment No. 7 is directed to the the methods of treatment that use compounds of formula IA wherein B is

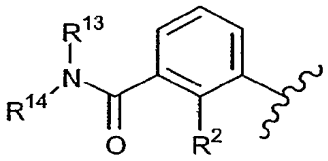


R^3 is selected from the group consisting of:



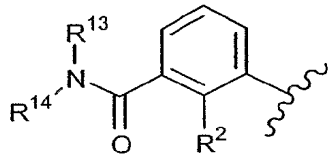
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 8 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



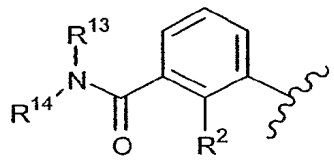
R^2, R^{13}, and R^{14} are as defined for compounds of formula IA, and all other substituents are as defined in formula IA.

Embodiment No. 9 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



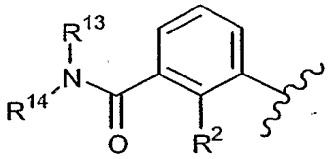
R^2 is –OH, R^{13} and R^{14} are as defined for compounds of formula and all other substituents are as defined in formula IA.

Embodiment No. 10 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is as defined for compounds of formula IA, R^{13} and R^{14} are the same or different alkyl group, and all other substituents areas defined for compounds of formula IA.

Embodiment No. 11 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is –OH, R^{13} and R^{14} are the same or different alkyl group, and all other substituents areas defined for compounds of formula IA.

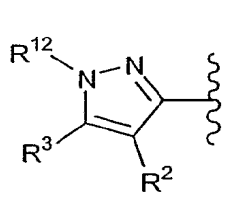
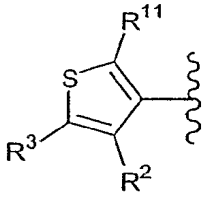
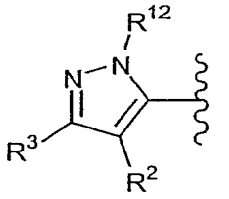
Embodiment No. 12 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in Embodiment No. 6, R^4 is H, R^5 is H, R^6 is H, and all other substituents areas defined for compounds of formula IA.

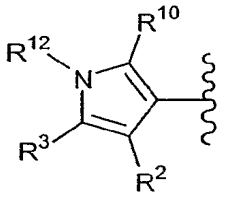
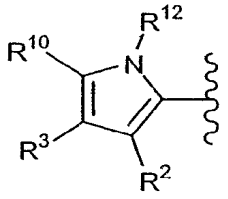
Embodiment No. 13 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in Embodiment No. 7, R^4 is H, R^5 is H, R^6 is H, and all other substituents areas defined for compounds of formula IA.

Embodiment No. 14 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in Embodiments Nos. 4, 5, 8 and

9, except that R^{13} and R^{14} are each methyl, and all other substituents are as defined in formula IA.

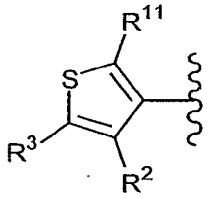
Embodiment No. 15 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:


,

,

,


and


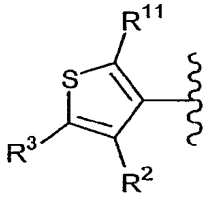
wherein all substituents are as defined for formula IA.

Embodiment No. 16 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



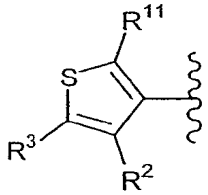
wherein all substituents are as defined for formula IA.

Embodiment No. 17 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



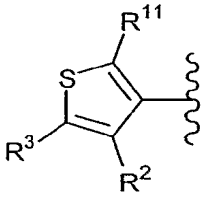
R^{11} is H, and all other substituents are as defined in formula IA.

Embodiment No. 18 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



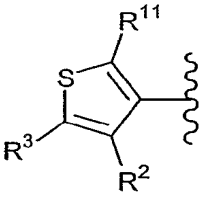
R^2 is –OH, and all other substituents are as defined in formula IA.

Embodiment No. 19 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



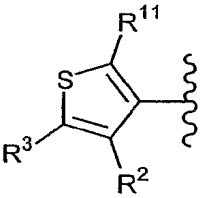
R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 20 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



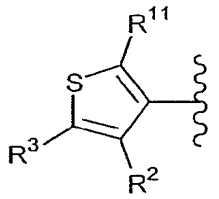
R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 21 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



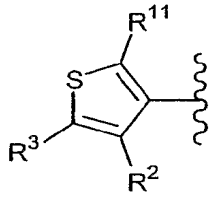
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, and all other substituents are as defined in formula IA.

Embodiment No. 22 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



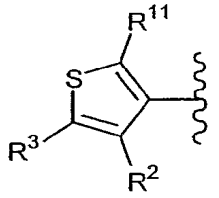
R^2 is –OH, and R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), and all other substituents are as defined in formula IA.

Embodiment No. 23 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



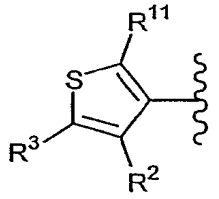
R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and all other substituents are as defined in formula IA.

Embodiment No. 24 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), each R^{13} and R^{14} are the same or different and are selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl). In this embodiment, each R^{13} and R^{14} are generally selected from the group consisting of: H and ethyl, and preferably R^{13} and R^{14} are ethyl.and all other substituents are as defined in formula IA.

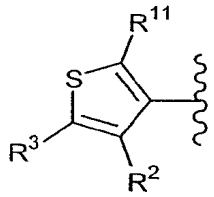
Embodiment No. 25 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and each R^{13} and R^{14} are the same or different and are selected from the group consisting of: H and alkyl (e.g., methyl, ethyl,

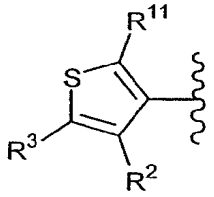
isopropyl and t-butyl). In this embodiment, each R^{13} and R^{14} are generally selected from the group consisting of: H and ethyl, and preferably R^{13} and R^{14} are ethyl.and all other substituents are as defined in formula IA.

Embodiment No. 26 is directed to the the methods of treatment that use compounds of formula IA wherein B is:

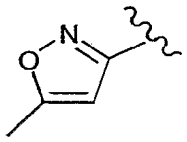


R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and all other substituents are as defined in formula IA.

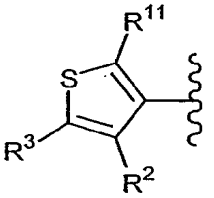
Embodiment No. 27 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is –OH, R^3 is $-C(O)NR^{13}R^{14}$, R^{11} is H, and R^{13} and R^{14} are independently selected from the group consisting of: alkyl, unsubstituted heteroaryl and substituted heteroaryl, and all other substituents are as defined in formula IA. In general, one of R^{13} or R^{14} is alkyl (e.g., methyl). An example of a substituted heteroaryl group is



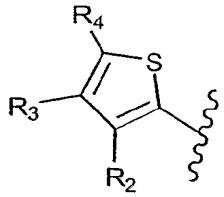
Embodiment No. 28 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



R^2 is –OH, R^3 is $-S(O)_tNR^{13}R^{14}$ (e.g., t is 2), R^{11} is H, and each R^{13} and R^{14} are the same or different and are selected from the group consisting of: H and alkyl (e.g., methyl, ethyl, isopropyl and t-butyl), and all other substituents are as defined in

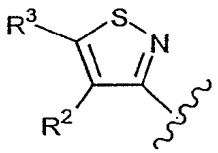
formula IA. In this embodiment, each R^{13} and R^{14} are generally selected from the group consisting of: H and ethyl, and preferably R^{13} and R^{14} are ethyl.

Embodiment No. 29 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



and all substituents are as defined in formula IA.

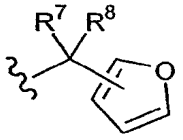
Embodiment No. 30 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



and all substituents are as defined in formula IA.

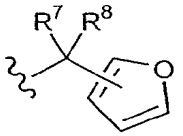
Embodiment No. 31 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is as described in any one of the Embodiment Nos. 39-44 described below.

Embodiment No. 32 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is:



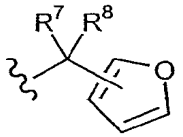
wherein the furan ring is unsubstituted or substituted as described in the definition of A for formula IA, and all other substituents are as defined for formula IA.

Embodiment No. 33 is directed to the the methods of treatment that use compounds of formula IA wherein B is described in any one of the Embodiment Nos. 1 to 30, and A is



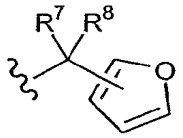
wherein the furan ring is substituted and all other substituents are as defined for formula IA.

Embodiment No. 34 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30,and A is



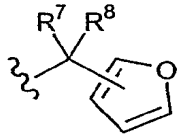
wherein the furan ring is substituted with at least one (e.g., 1 to 3, or 1 to 2) alkyl group and all other substituents are as defined for formula IA.

Embodiment No. 35 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, A is



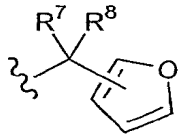
wherein the furan ring is substituted with one alkyl group and all other substituents are as defined for formula IA.

Embodiment No. 36 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is



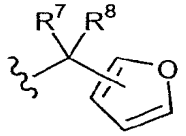
wherein the furan ring is substituted with one C_1 to C_3 alkyl group (e.g., methyl or isopropyl), and all other substituents are as defined for formula IA.

Embodiment No. 37 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is



as defined in any one of the Embodiment Nos. 32 to 36, except that R^7 and R^8 are the same or different and each is selected from the group consisting of: H and alkyl.

Embodiment No. 38 is directed to the the methods of treatment that use compounds of formula IA wherein B is as described in any one of the Embodiment Nos. 1 to 30, and A is

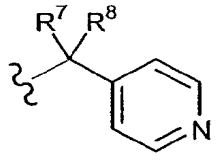
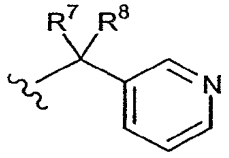
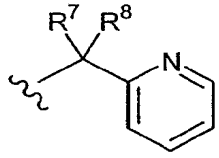


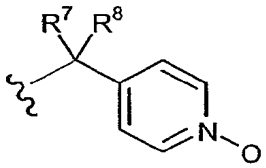
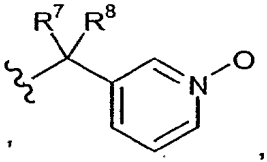
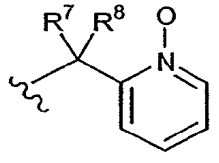
as defined in any one of the Embodiment Nos. 32 to 36, except that R^7 is H, and R^8 is alkyl (e.g., ethyl or t-butyl).

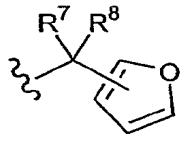
Embodiment No. 39 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is preferably selected from the group consisting of:

(a)


,

,

,


,

,

,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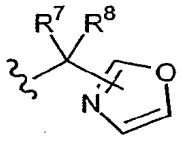
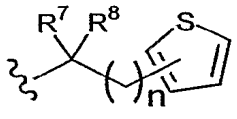
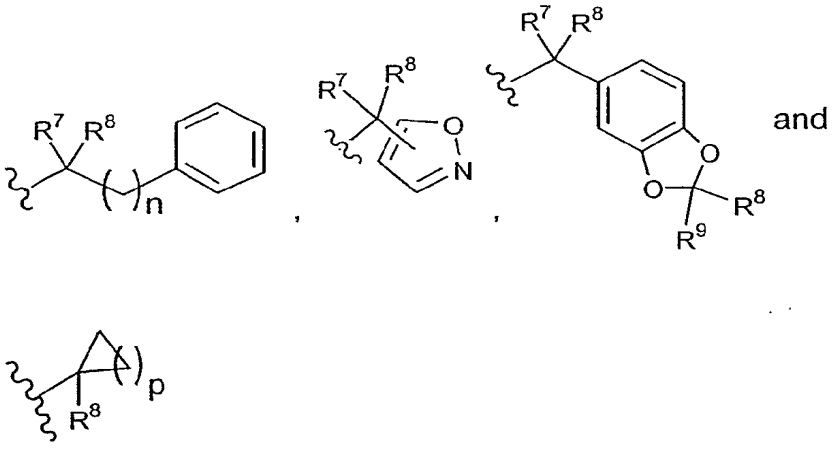
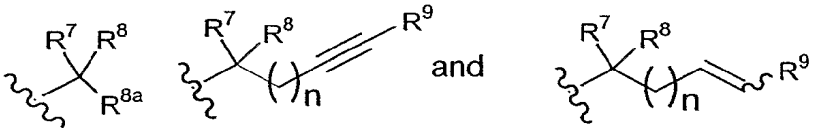

,

,



wherein the above rings are unsubstituted or substituted, as described for formula IA: and

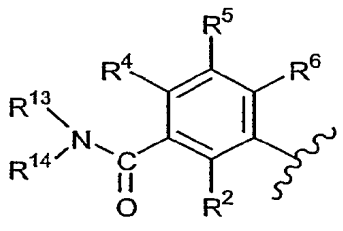
(b)

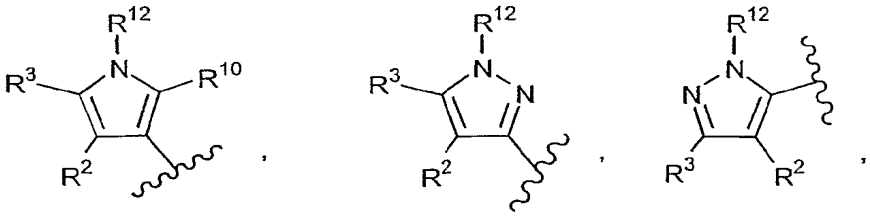


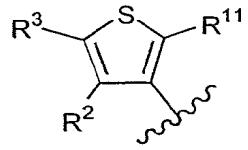
, and

wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is preferably selected from the group consisting of:





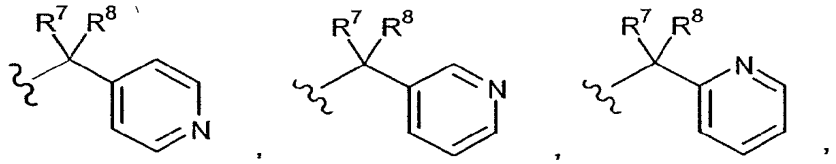
and 

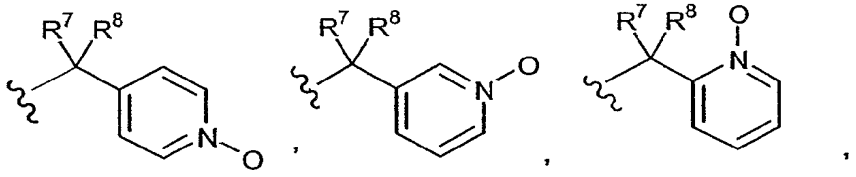
wherein R^2 to R^6 and R^{10} to R^{14} are as defined above for the novel compounds of formula IA .

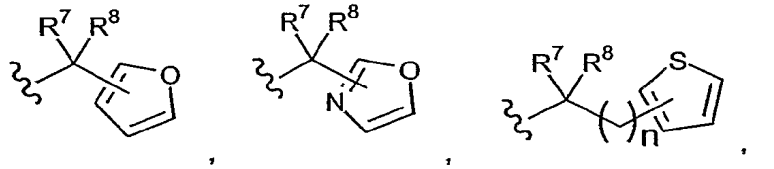
Embodiment No. 40 is directed to the the methods of treatment that use compounds of formula IA wherein:

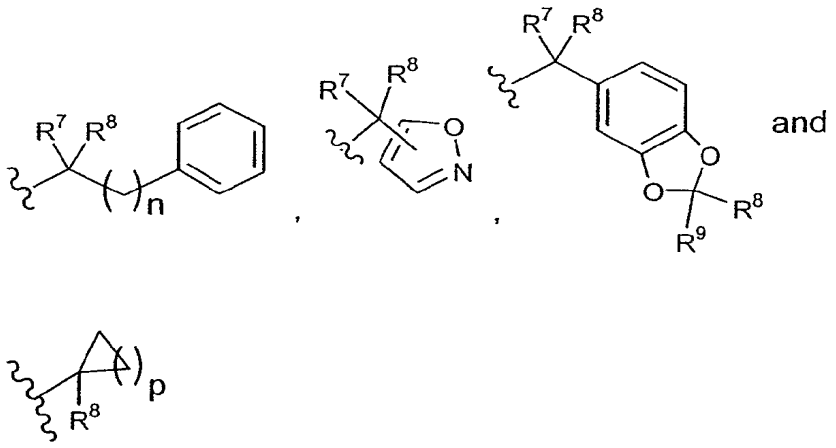
(1) substituent A in formula IA is more preferably selected from the group consisting of:

(a)



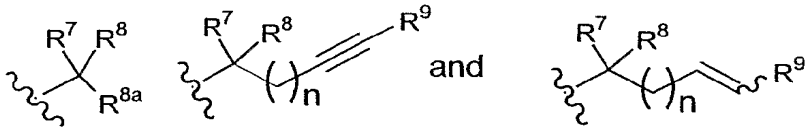






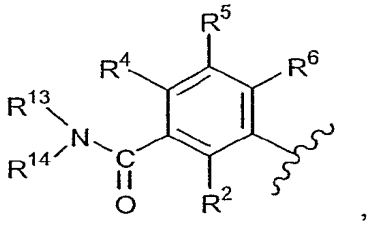
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; and

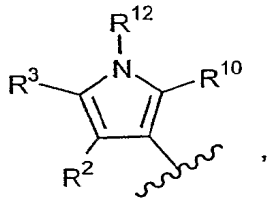
(b)

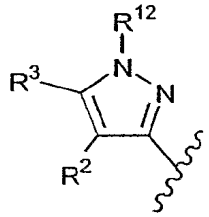


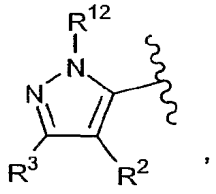
wherein each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); wherein R^{8a} is as defined in formula IA, and wherein R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and

(2) substituent B in formula IA is more preferably selected from the group consisting of:

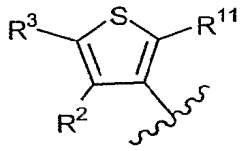








and



wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$, halogen, and $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano;

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

each R^{10} and R^{11} is independently selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

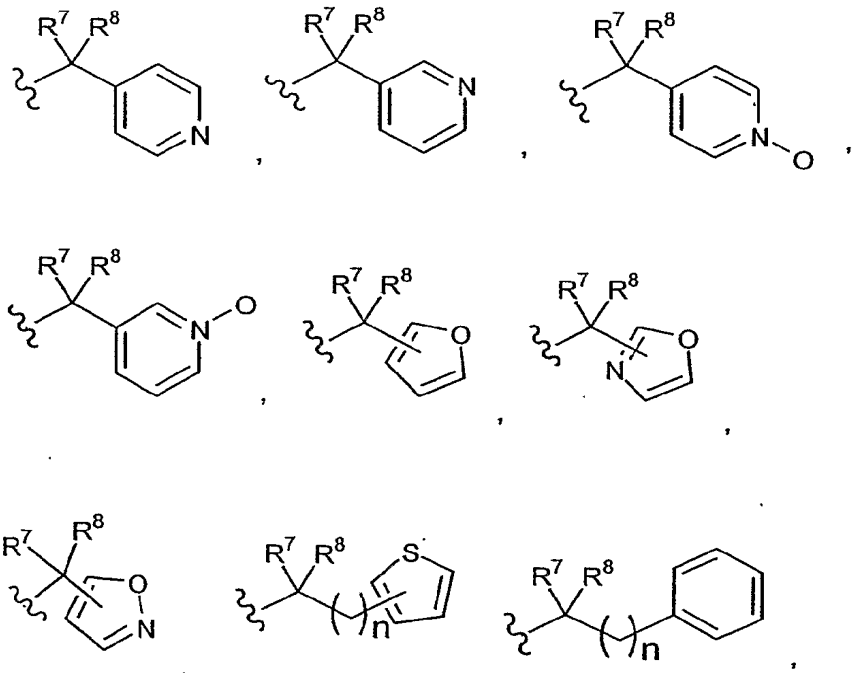
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional

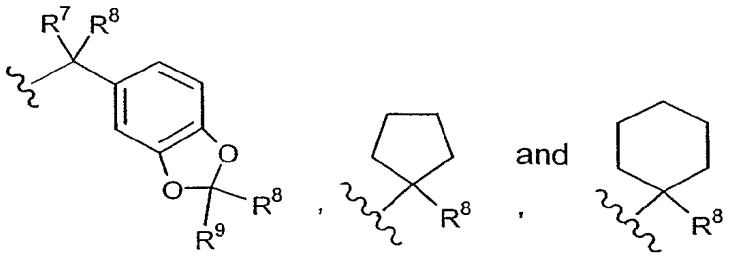
heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 41 is directed to the the methods of treatment that use compounds of formula IA wherein:

substituent A in formula IA is even more preferably selected from the group consisting of:

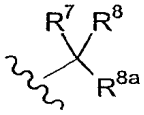
(a)





wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^9 is selected from the group consisting of: H, F, Cl, Br, alkyl or $-CF_3$; and

(b)

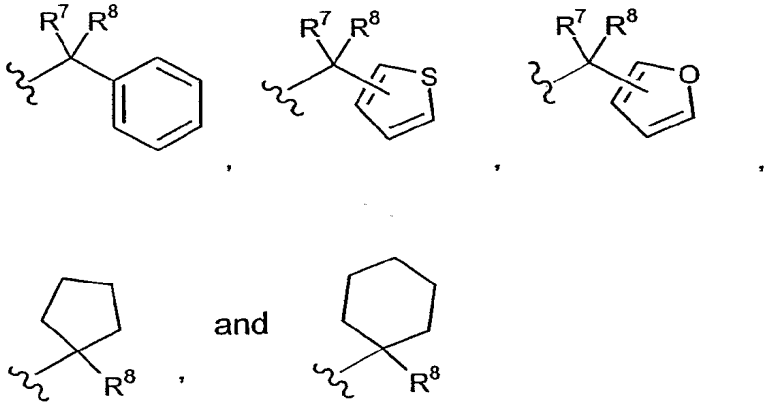


wherein R^7 is selected from the group consisting of: H, fluoroalkyl, alkyl and cycloalkyl; R^8 is selected form the group consisting of: H, alkyl, $-CF_2CH_3$ and $-CF_3$; and R^{8a} is as defined for formula IA.

Embodiment No. 42 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is still even more preferably selected from the group consisting of:

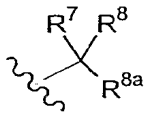
(a)



wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl,

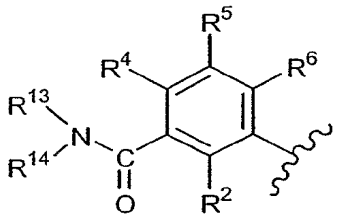
cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)

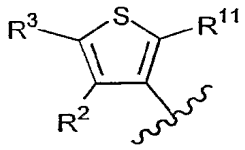


wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

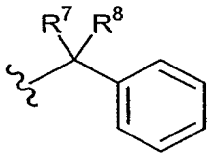
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 43 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is yet even still more preferably selected from the group consisting of:

(a)



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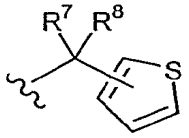

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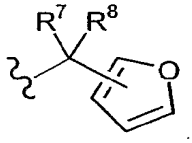

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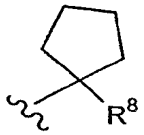
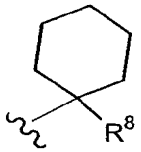
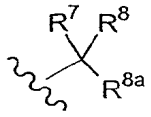


,
and


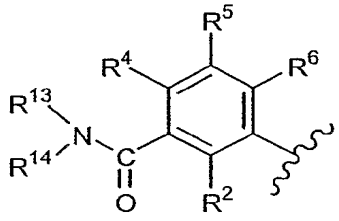
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)

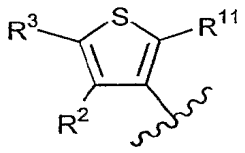


wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

(2) substituent B in formula IA is yet even still more preferably selected from the group consisting of:



, and



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$ $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

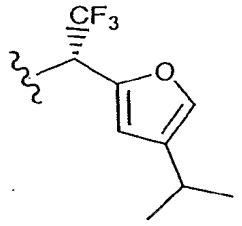
R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: methyl and ethyl.

Embodiment No. 44 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is most preferably selected from the group consisting of:



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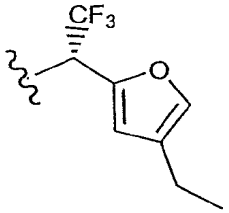

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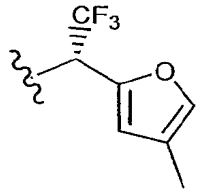

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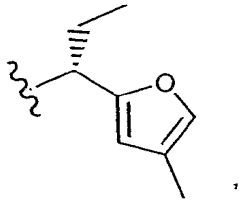

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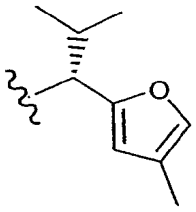

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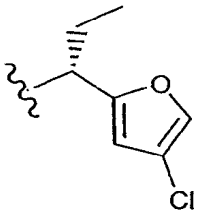

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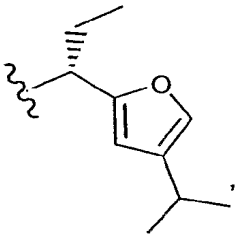

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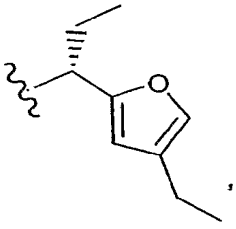

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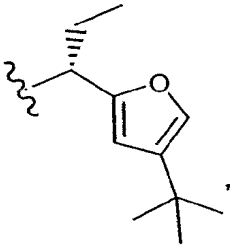

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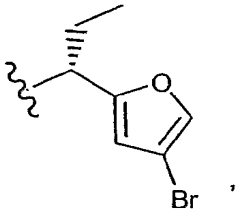

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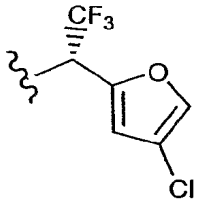

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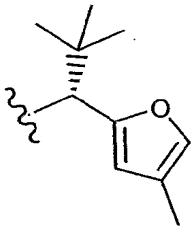

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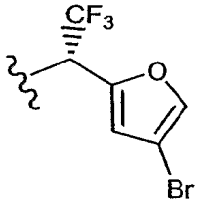

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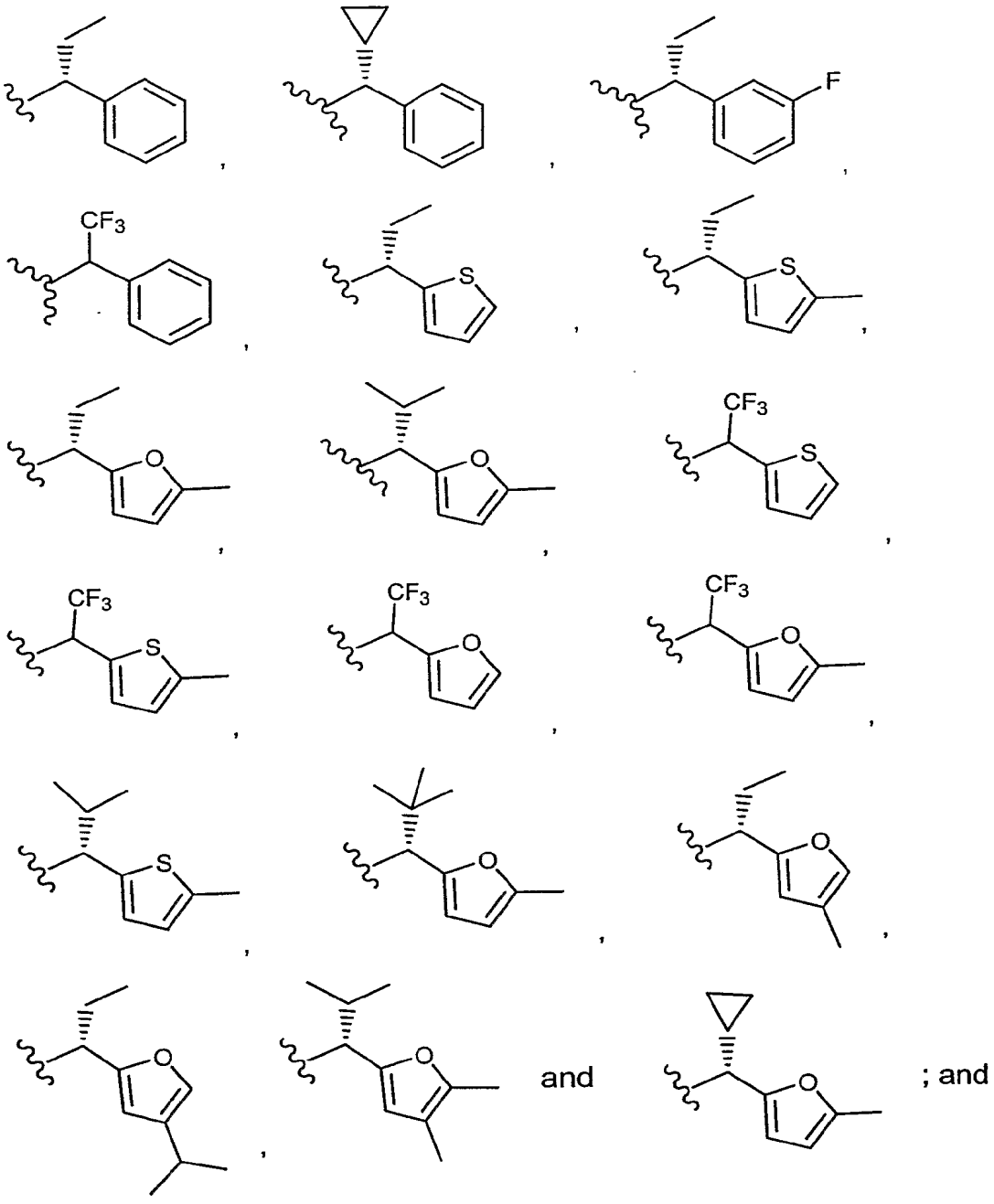
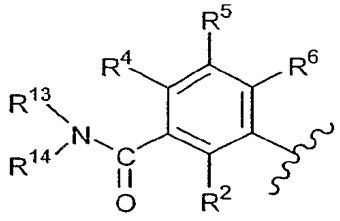
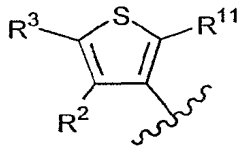


and ; and

(2) substituent B in formula IA is most preferably selected from the group consisting of:



and



wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

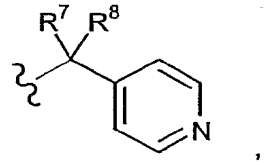
R^{11} is H; and

R^{13} and R^{14} are methyl.

Embodiment No. 45 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)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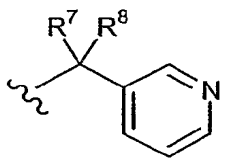
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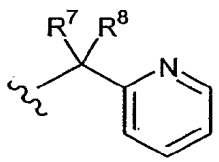
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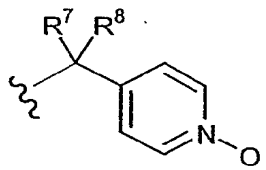
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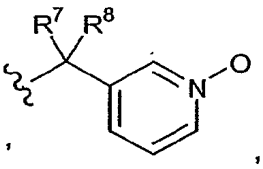
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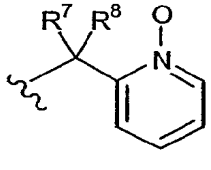
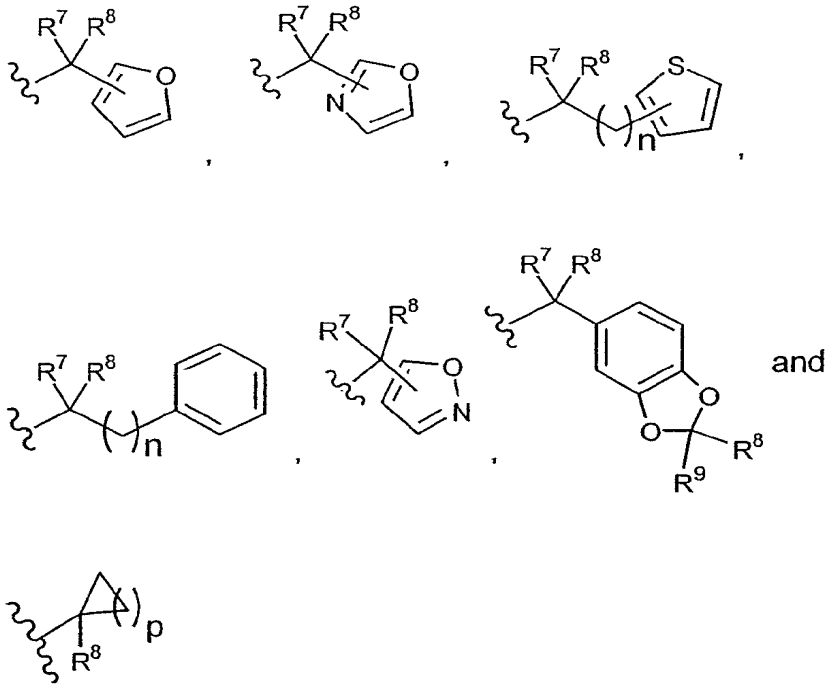
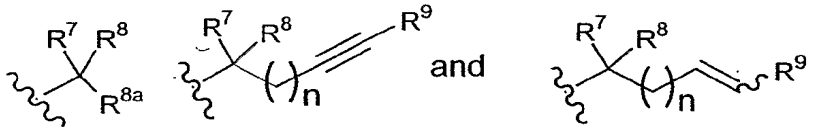

;



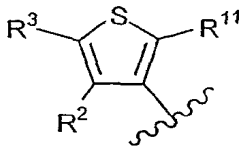
wherein the above rings are unsubstituted or substituted, as described for formula IA: and

(b)



wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is:

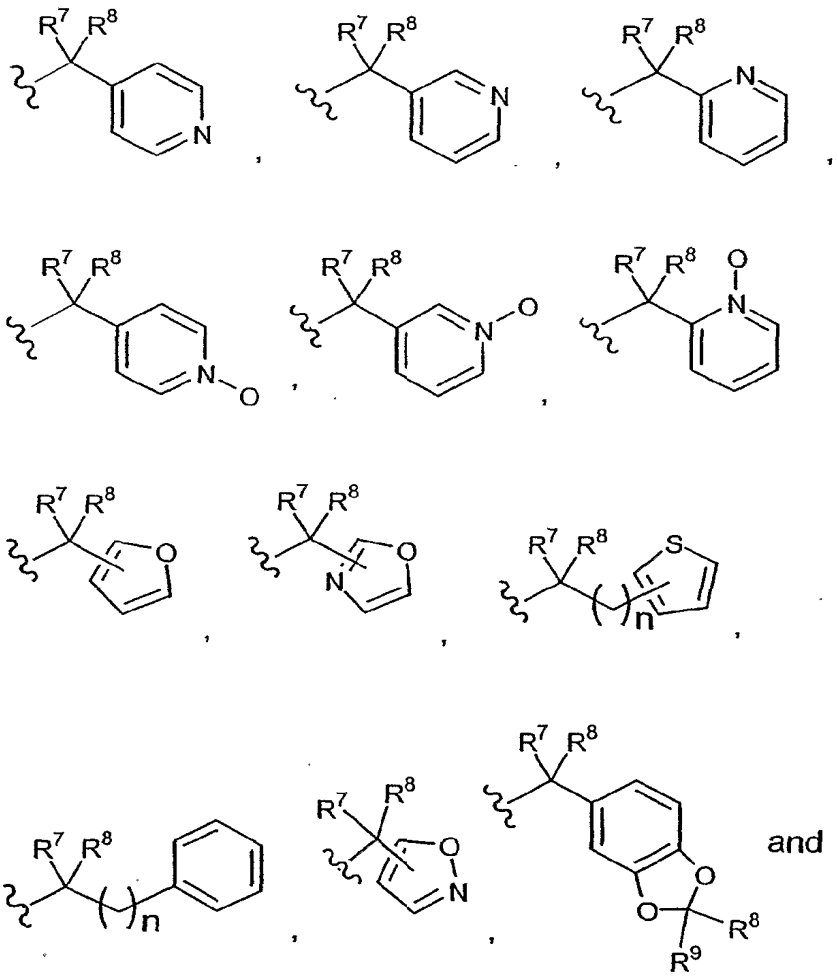


wherein R^2, R^3 and R^{11} are as defined above for the novel compounds of formula IA .

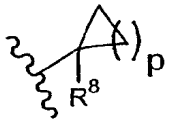
Embodiment No. 46 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

(a)

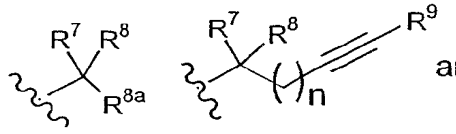


and



wherein the above rings are unsubstituted or substituted, as described for formula IA: and

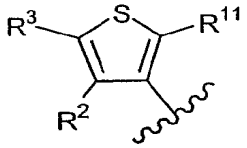
(b)



, and

wherein in (a) and (b) above: each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, fluoroalkyl, alkynyl, alkenyl, and cycloalkenyl, wherein said substituents on said R^7 and R^8 substituted groups are selected from the group consisting of: a) cyano, b) $-CO_2R^{13}$, c) $-C(O)NR^{13}R^{14}$, d) $-SO_2NR^{13}R^{14}$, e) $-NO_2$, f) $-CF_3$, g) $-OR^{13}$, h) $-NR^{13}R^{14}$, i) $-OC(O)R^{13}$, j) $-OC(O)NR^{13}R^{14}$, and k) halogen; and R^{8a} and R^9 are as defined in formula IA; and

(2) substituent B in formula IA is:



R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^{11} is selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

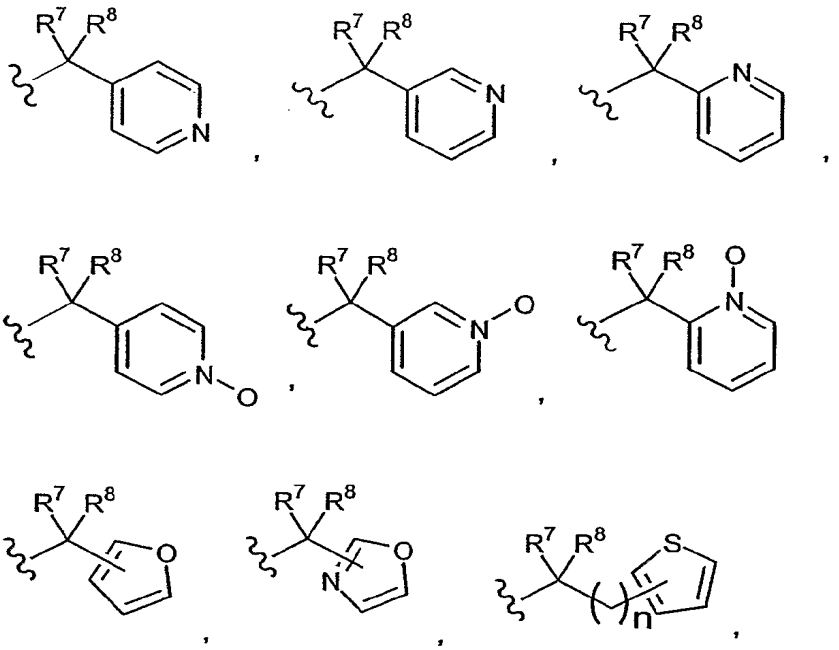
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$, form an unsubstituted or substituted

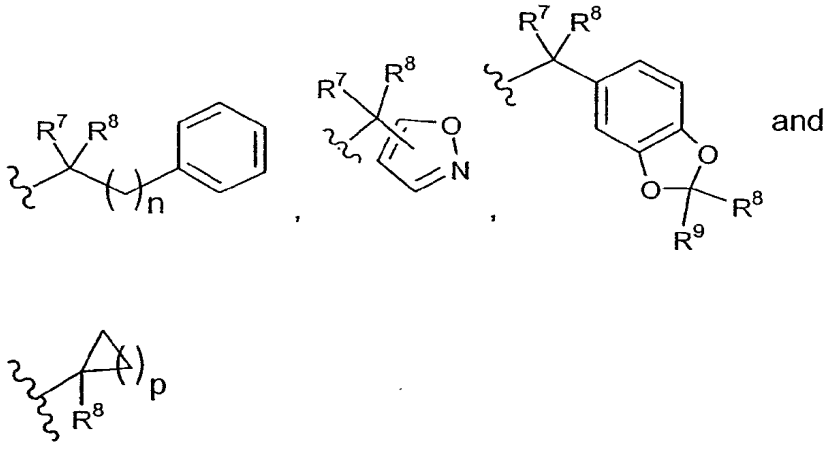
saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 47 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

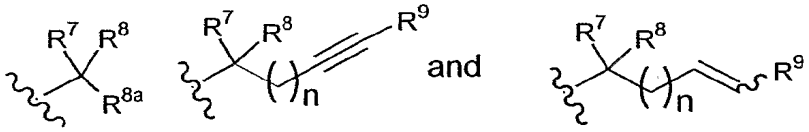
(a)





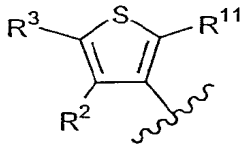
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; and

(b)



wherein each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); wherein R^{8a} is as defined in formula IA, and wherein R^9 is selected from the group consisting of: H, halogen, alkyl, cycloalkyl, $-CF_3$, cyano, $-OCH_3$, and $-NO_2$; each R^7 and R^8 is independently selected from the group consisting of: H, alkyl (e.g., methyl, ethyl, t-butyl, and isopropyl), fluoroalkyl (such as, $-CF_3$ and $-CF_2CH_3$), cycloalkyl (e.g.,cyclopropyl, and cyclohexyl), and cycloalkylalkyl (e.g., cyclopropylmethyl); and

(2) substituent B in formula IA is:



wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ or and $-NHSO_2R^{13}$;

R^3 is $-SO_2NR^{13}R^{14}$;

R^{11} is selected from the group consisting of: R^{13}, hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

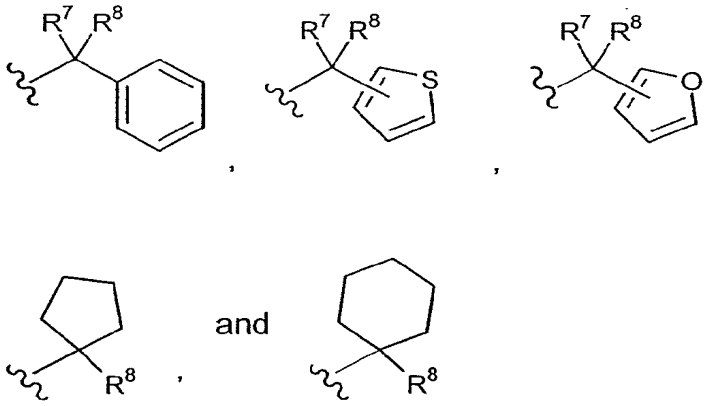
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

R^{13} and R^{14} when taken together with the nitrogen they are attached to in the group $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

Embodiment No. 48 is directed to the the methods of treatment that use compounds of formula IA wherein:

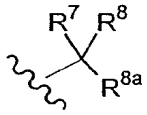
(1) substituent A in formula IA is selected from the group consisting of:

(a)



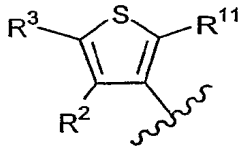
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: H, F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA.

(2) substituent B in formula IA is:



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

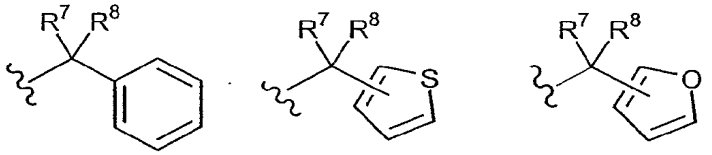
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

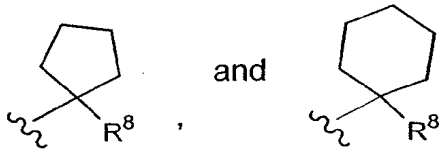
each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl.

Embodiment No. 43 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

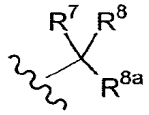
(a)





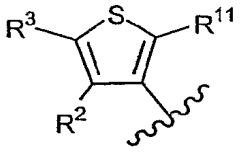
wherein the above rings are unsubstituted, or the above rings are substituted with 1 to 3 substituents independently selected from the group consisting of: F, Cl, Br, alkyl, cycloalkyl, and $-CF_3$; R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and

(b)



wherein R^7 is selected from the group consisting of: H, $-CF_3$, $-CF_2CH_3$, methyl, ethyl, isopropyl, cyclopropyl and t-butyl; and R^8 is H; and R^{8a} is as defined for formula IA;

(2) substituent B in formula IA is:



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$ (preferably –OH);

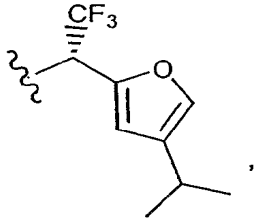
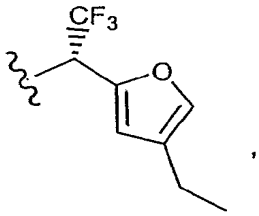
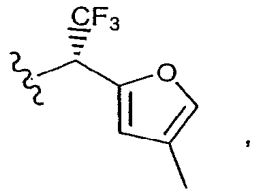
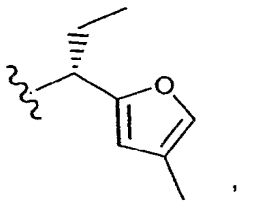
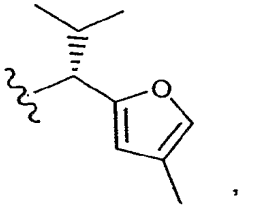
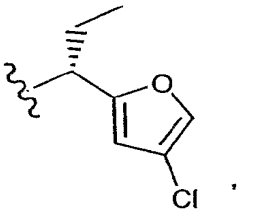
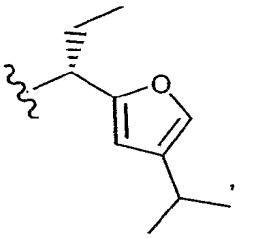
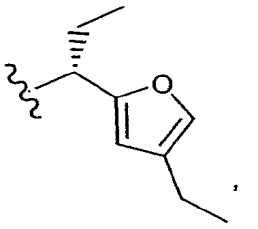
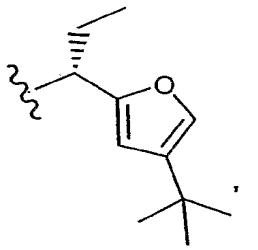
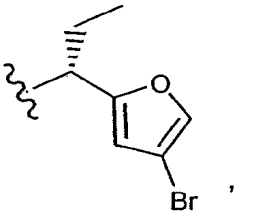
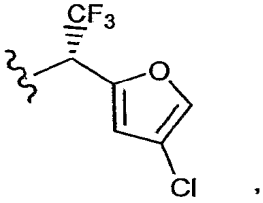
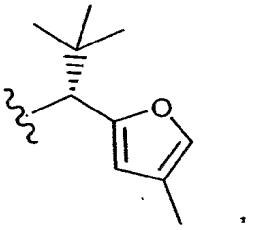
R^3 is $-SO_2NR^{13}R^{14}$;

R^{11} is selected from the group consisting of: H, halogen and alkyl (preferably H); and

each R^{13} and R^{14} is independently selected from the group consisting of: H and ethyl, preferably R^{13} and R^{14} are ethyl.

Embodiment No. 50 is directed to the the methods of treatment that use compounds of formula IA wherein:

(1) substituent A in formula IA is selected from the group consisting of:

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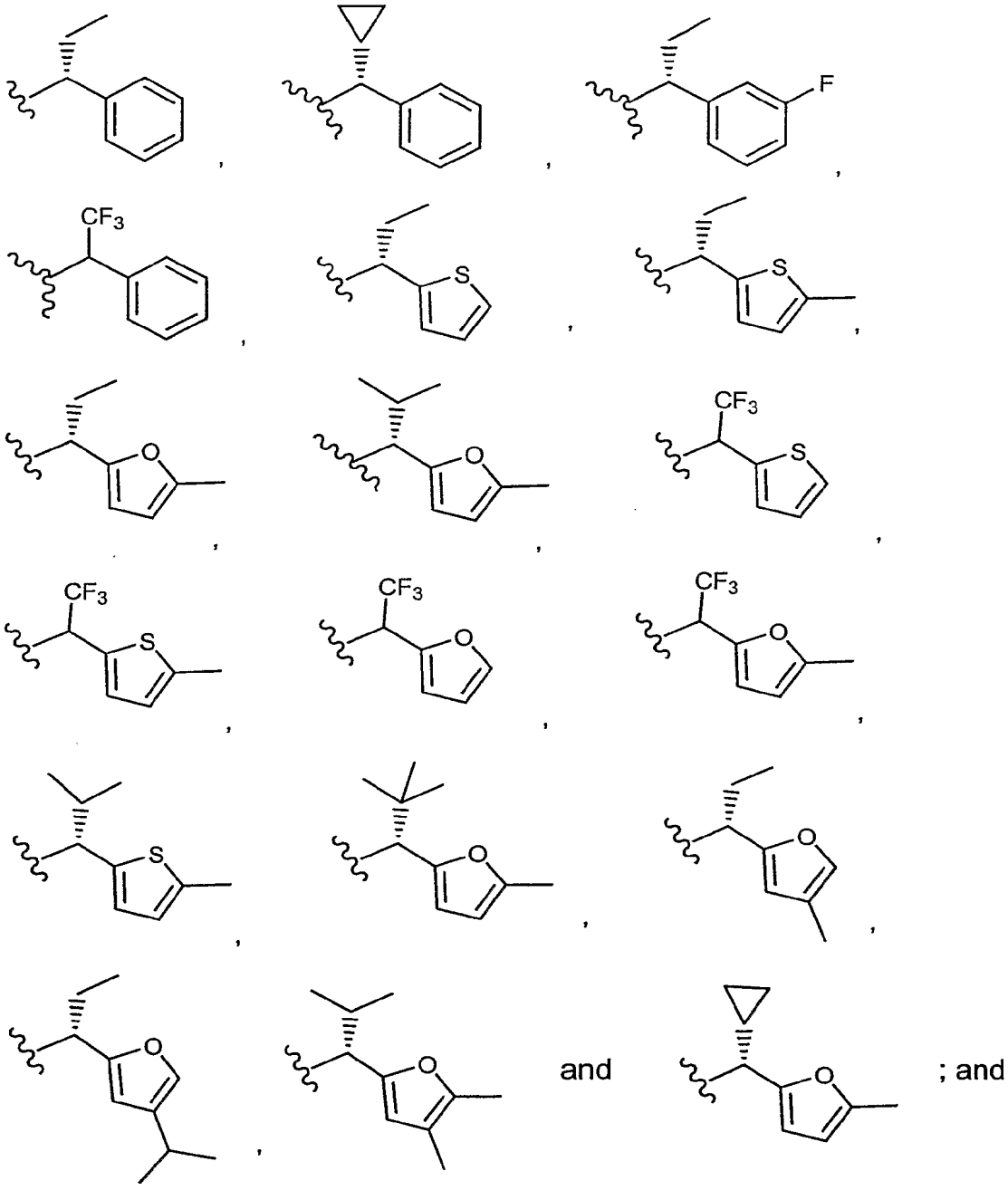
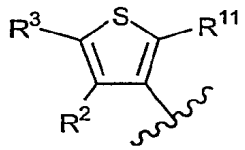


and ; and

(2) substituent B in formula IA is:



wherein:

R^2 is –OH;

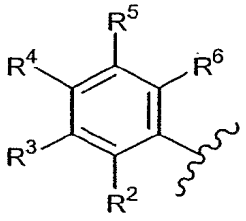
R^3 is: $-SO_2NR^{13}R^{14}$;

R^{11} is H; and

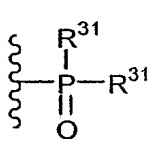
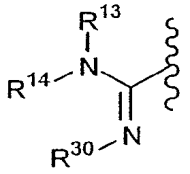
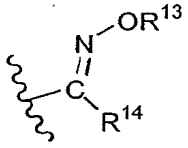
R^{13} and R^{14} are ethyl.

Embodiment No. 51 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:

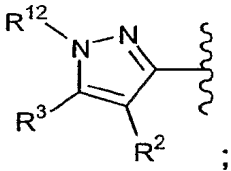
(1)



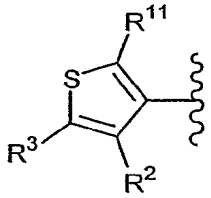
provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,


,

and

;

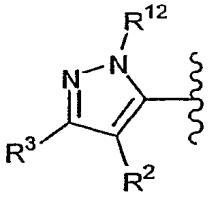
(2)


;

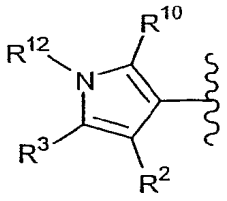
(3)


;

(4)

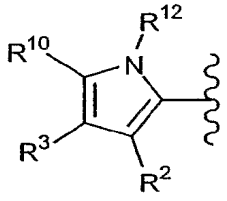

;

(5)



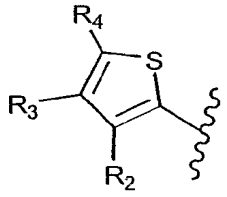
;

(6)



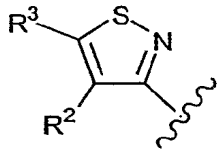
;

(7)



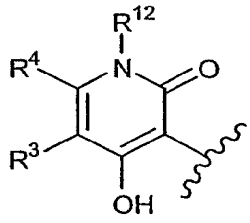
;

(8)



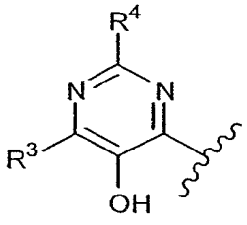
;

(9)



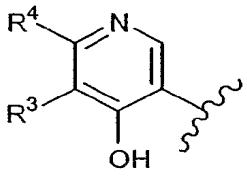
;

(10)



;

(11)



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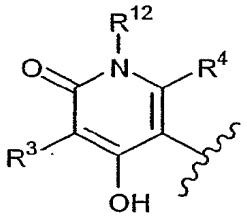
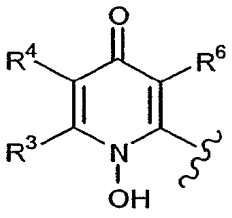
(12)



; and

(13)

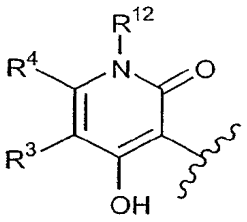


;

wherein all other substituents are as defined for formula IA.

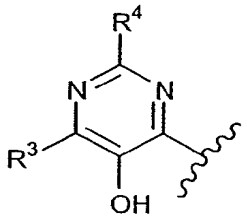
Embodiment No. 52 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:

(1)



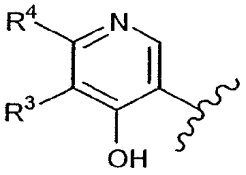
;

(2)



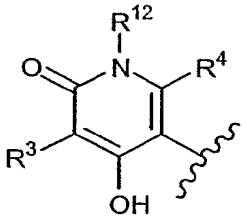
;

(3)



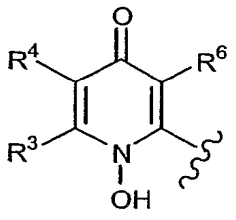
;

(4)



; and

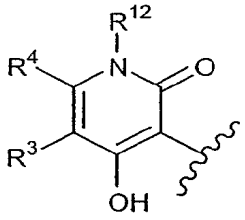
(5)



;

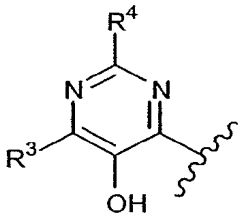
wherein all substituents are as defined for formula IA.

Embodiment No. 53 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



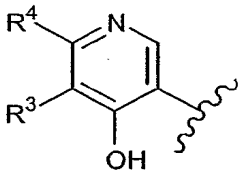
wherein all substituents are as defined for formula IA.

Embodiment No. 54 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



wherein all substituents are as defined for formula IA.

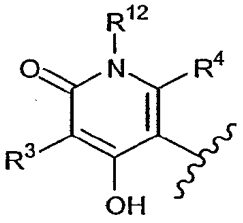
Embodiment No. 55 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



;

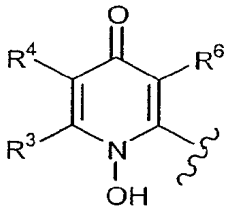
wherein all substituents are as defined for formula IA.

Embodiment No. 56 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



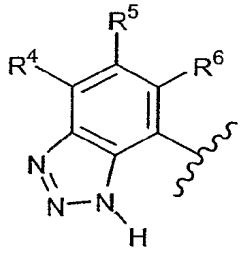
wherein all substituents are as defined for formula IA.

Embodiment No. 57 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



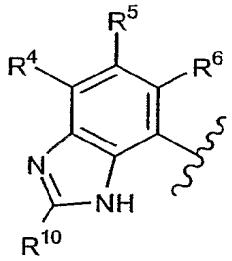
wherein all substituents are as defined for formula IA.

Embodiment No. 58 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



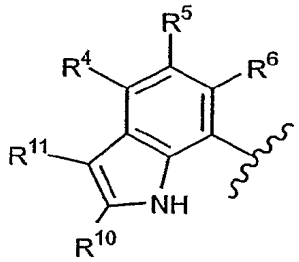
wherein all substituents are as defined for formula IA.

Embodiment No. 59 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



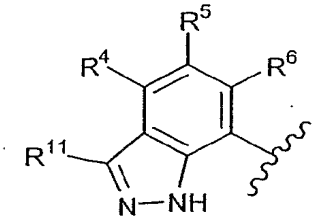
wherein all substituents are as defined for formula IA.

Embodiment No. 60 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



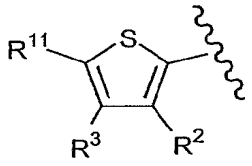
wherein all substituents are as defined for formula IA.

Embodiment No. 61 is directed to the the methods of treatment that use compounds of formula IA wherein B is:



wherein all substituents are as defined for formula IA.

Embodiment No. 62 is directed to the the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:



wherein all substituents are as defined for formula IA.

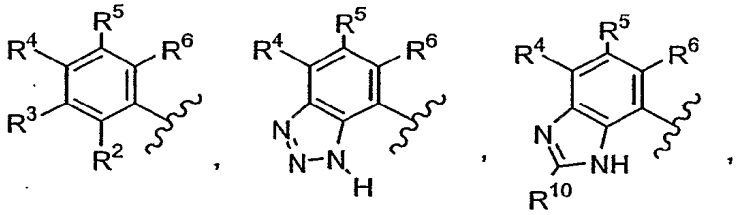
Embodiment No. 63 is directed to the the methods of treatment that use compounds of formula IA wherein B is described in any of Embodiment Nos. 51 to 62 and A is as described in any of Embodiments Nos. 32-44.

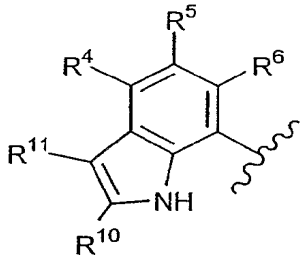
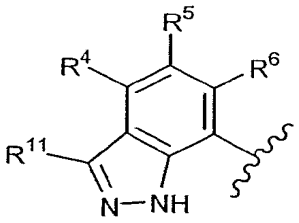
Embodiment No. 64 is directed to any one of the Embodiment Nos. 1 to 63 wherein the compound of formula IA is a pharmaceutically acceptable salt.

Embodiment No. 65 is directed to any one of the Embodiment Nos. 1 to 63 wherein the compound of formula IA is a sodium salt.

Embodiment No. 66 is directed to any one of the Embodiment Nos. 1 to 63 wherein the compound of formula IA is a calcium salt.

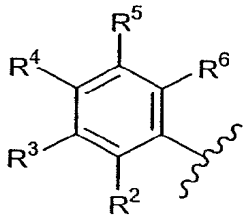
Embodiment No. 67 is directed to the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:




and


wherein all substituents are as defined for formula IA.

Embodiment No. 68 is directed to the methods of treatment that use compounds of formula IA wherein B is selected from the group consisting of:



wherein:

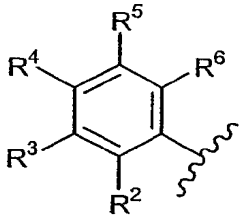
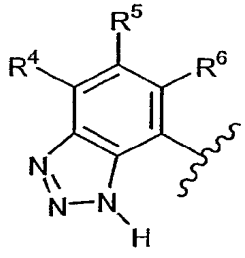
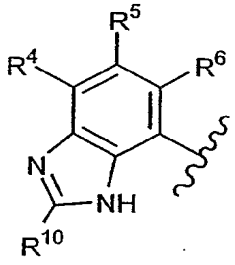
R^2, R^4, R^5 and R^6 are as defined for formula IA; and

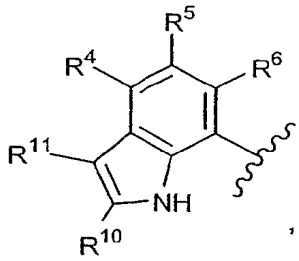
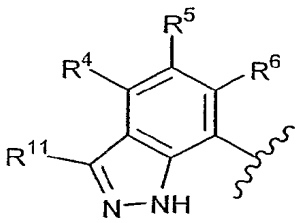
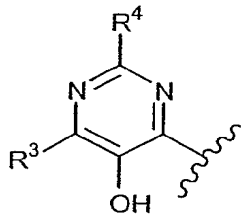
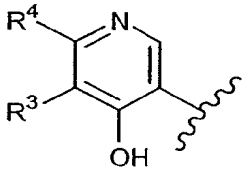
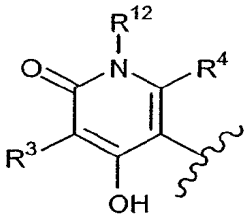
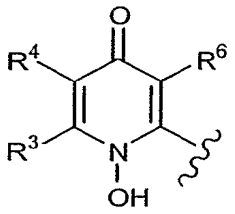
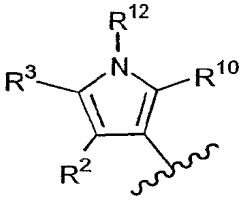
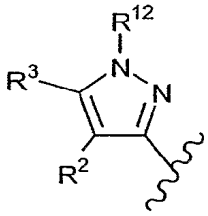
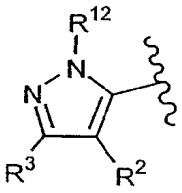
R^3 is selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups.

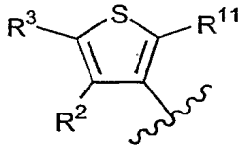
Embodiment No. 69 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 39; and

(2) substituent B in formula IA is preferably selected from the group consisting of:


,

,

,

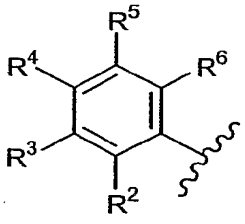
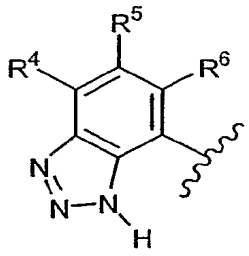
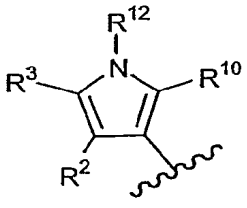
and 

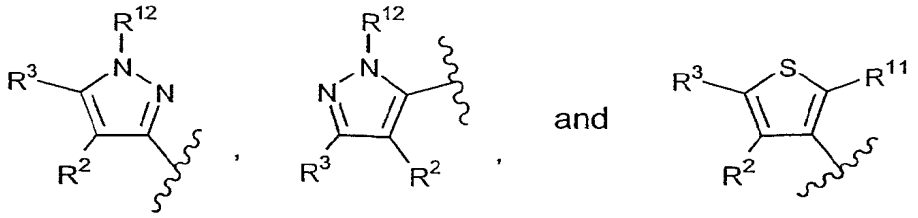
wherein R^2 to R^6 and R^{10} to R^{14} are as defined for formula IA.

Embodiment No. 70 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 40; and

(2) substituent B in formula IA is more preferably selected from the group consisting of:



wherein

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ or and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, $-C(O)NR^{13}R^{14}$, $-SO_2R^{13}$; and $-C(O)OR^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$, halogen, and $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano;

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

each R^{10} and R^{11} is independently selected from the group consisting of: hydrogen, halogen, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$,$-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$, $-COR^{13}$, $-OR^{13}$, and cyano;

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

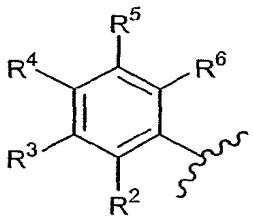
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-SO_2NR^{13}R^{14}$, $-OC(O)NR^{13}R^{14}$, $-CONR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-SO_tNR^{13}R^{14}$, $-NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from the group consisting of: O, S or NR^{18}; wherein R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$; wherein each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., the substituents on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$,

-C(O)$NR^{15}R^{16}$, -$SO_tNR^{15}R^{16}$, -C(O)R^{15}, -SO_2R^{15} provided that R^{15} is not H, -NHC(O)$NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting: of H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

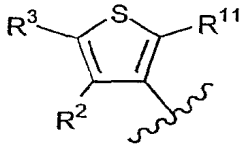
Embodiment No. 71 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 42; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, -NHC(O)R^{13} and -$NHSO_2R^{13}$;

R^3 is selected from the group consisting of: -C(O)$NR^{13}R^{14}$, -$SO_2NR^{13}R^{14}$, -NO_2, cyano, -SO_2R^{13}; and -C(O)OR^{13};

R^4 is selected from the group consisting of: H, -NO_2, cyano, -CH_3 or -CF_3;

R^5 is selected from the group consisting of: H, -CF_3, -NO_2, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and -CF_3;

R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl; or

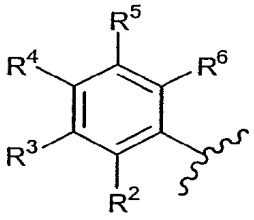
R^{13} and R^{14} when taken together with the nitrogen they are attached to in the groups -$NR^{13}R^{14}$, -C(O)$NR^{13}R^{14}$, -$SO_2NR^{13}R^{14}$, -OC(O)$NR^{13}R^{14}$, -$CONR^{13}R^{14}$, -$NR^{13}C(O)NR^{13}R^{14}$, -$SO_tNR^{13}R^{14}$, -$NHSO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring (preferably a 3 to 7 membered ring) optionally having one additional heteroatom selected from O, S or NR^{18} wherein R^{18} is selected from H, alkyl, aryl, heteroaryl, -C(O)R^{19}, -SO_2R^{19} and -C(O)$NR^{19}R^{20}$, wherein each R^{19} and R^{20} is independently selected from alkyl, aryl and heteroaryl, wherein there are 1

to 3 substituents on the substituted cyclized R^{13} and R^{14} groups (i.e., on the ring formed when R^{13} and R^{14} are taken together with the nitrogen to which they are bound) and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$ and halogen; and wherein each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl.

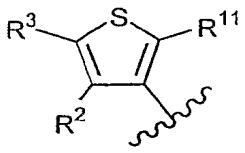
Embodiment No. 72 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 43; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



and



wherein:

R^2 is selected from the group consisting of: H, OH, $-NHC(O)R^{13}$ and $-NHSO_2R^{13}$;

R^3 is selected from the group consisting of: $-C(O)NR^{13}R^{14}$ $-SO_2NR^{13}R^{14}$, $-NO_2$, cyano, and $-SO_2R^{13}$;

R^4 is selected from the group consisting of: H, $-NO_2$, cyano, $-CH_3$ or $-CF_3$;

R^5 is selected from the group consisting of: H, $-CF_3$, $-NO_2$, halogen and cyano; and

R^6 is selected from the group consisting of: H, alkyl and $-CF_3$;

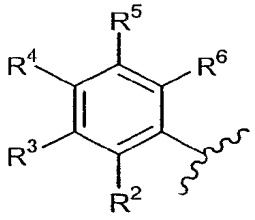
R^{11} is selected from the group consisting of: H, halogen and alkyl; and

each R^{13} and R^{14} is independently selected from the group consisting of: methyl and ethyl.

Embodiment No. 73 is directed to the methods of treatment that use compounds of formula IA wherein:

(1) substituent A is as defined in Embodiment No. 44; and

(2) substituent B in formula IA is preferably selected from the group consisting of:



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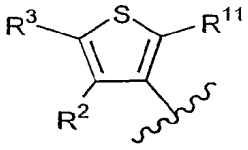


wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{11} is H; and

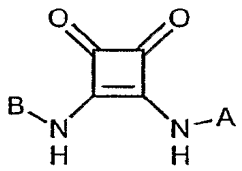
R^{13} and R^{14} are methyl.

Embodiment No. 74 is directed to any one of the Embodiment Nos. 67 to 73 wherein the compound of formula IA is a pharmaceutically acceptable salt.

Embodiment No. 75 is directed to any one of the Embodiment Nos. 67 to 73 wherein the compound of formula IA is a sodium salt.

Embodiment No. 76 is directed to any one of the Embodiment Nos. 1 to 73 wherein the compound of formula IA is a calcium salt.

This invention is also directed to novel compounds of formula IB:

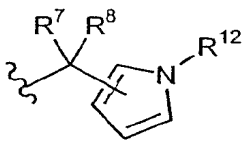


(IB)

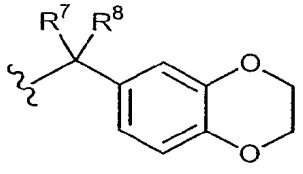
and the pharmaceutically acceptable salts (e.g., sodium or calcium salt) and solvates thereof, wherein:

A is selected from the group consisting of:

(1)

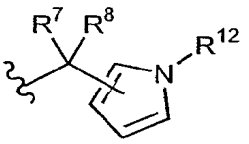


and



; and

(2)



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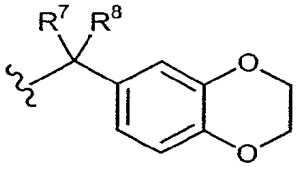


wherein said rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups; and

Substituents B, R^7, R^8, R^9 and R^{12} are as defined for formula IA.

Thus, for compounds of formula IB, substituents B, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{30}, R^{31}, R^{40}, q, and t are as defined for formula IA.

In other embodiments of the compounds of formula IB, substituent B is as defined in anyone of Embodiments 1 to 30 described above.

In other embodiments of the compounds of formula IB, substituent B is as defined in anyone of Embodiments 51 to 62 described above.

In other embodiments of the compounds of formula IB, substituent B is as defined in anyone of Embodiments 67 to 73 described above.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least one (e.g., one) compound of formula IB and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to the calcium salts of the compounds of formula IB.

Another embodiment of this invention is directed to the sodium salts of the compounds of formula IB.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least one (e.g., one) sodium salt of a compound of formula IB and a pharmaceutically acceptable carrier.

Another embodiment of this invention is directed to a pharmaceutical composition comprising at least one (e.g., one) calcium salt of a compound formula IB and a pharmaceutically acceptable carrier.

The chemokine mediated diseases, that are treated by administering at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt or solvate of said compounds, include: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy,

periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

The chemokine mediated diseases, that are treated by administering at least one (e.g., one) compound of formula IB, include: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

Another embodiment of this invention is directed to a method of treating acute inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least

one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating acute neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IA (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating acute inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating chronic inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating acute neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of

such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating COPD in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

Another embodiment of this invention is directed to a method of treating acute inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic inflammatory pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating acute neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least

one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating chronic neuropathic pain in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

Another embodiment of this invention is directed to a method of treating COPD in a patient (e.g., a mammal, preferably a human being) in need of such treatment comprising administering to said patient an effective amount of at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof).

An embodiment of the present invention is directed to a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering to said patient, concurrently or sequentially, a therapeutically effective amount of (a) at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and (b) a microtubule affecting agent or antineoplastic agent or anti-angiogenesis agent or VEGF receptor kinase inhibitor or antibodies against the VEGF receptor or interferon, and/or c) radiation.

In further embodiments directed to the treatment of cancer, at least one (e.g., one) compound selected from the group consisting of compounds of the 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), is administered in combination with antineoplastic agents (e.g., one or more, such as one, or such as one or two), selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, taxotere and Vincristine.

In another embodiment the present invention provides a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering, concurrently or sequentially, an effective amount

of (a) at least one (e.g., one) compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and (b) a microtubule affecting agent (*e.g.,* paclitaxel).

An embodiment of the present invention is directed to a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering to said patient, concurrently or sequentially, a therapeutically effective amount of (a) at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof), and (b) a microtubule affecting agent or antineoplastic agent or anti-angiogenesis agent or VEGF receptor kinase inhibitor or antibodies against the VEGF receptor or interferon, and/or c) radiation.

In further embodiments directed to the treatment of cancer, at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof) is administered in combination with antineoplastic agents (e.g., one or more, such as one, or such as one or two), selected from the group consisting of: gemcitabine, paclitaxel (Taxol®), 5-Fluorouracil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, taxotere and Vincristine.

In another embodiment the present invention provides a method of treating cancer in a patient (e.g., a mammal, such as a human being) in need of such treatment, comprising administering, concurrently or sequentially, an effective amount of (a) at least one (e.g., 1-3, and usually one) compound of formula IB (or a pharmaceutically acceptable salt or solvate thereof), and (b) a microtubule affecting agent (*e.g.,* paclitaxel).

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound of formula IB (or a pharmaceutically acceptable salt or solvate of said compound).

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective

amount of at least one (e.g., one) compound of formula IB (or a pharmaceutically acceptable salt or solvate of said compound), in combination with administering at least one anticancer agent.

Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound of formula IB (or a pharmaceutically acceptable salt or solvate of said compound), in combination with administering at least one anticancer agent, wherein said anticancer agent is selected from the group consisting of: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids, and synthetics.

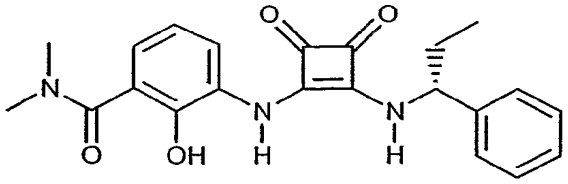
Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

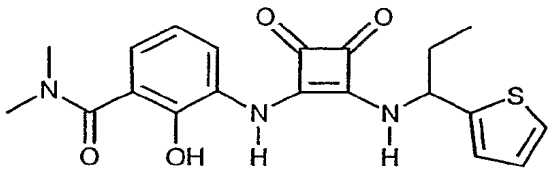
Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), in combination with administering at least one anticancer agent.

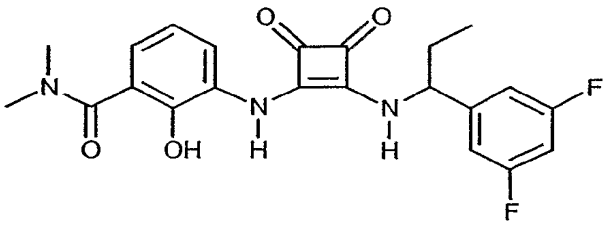
Another embodiment of this invention is directed to a method of treating melanoma, gastric carcinoma, and non-small cell lung cancer in a patient in need of such treatment, said treatment comprising administering to said patient an effective amount of at least one (e.g., one) compound selected from the group consisting of the compounds of formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), in combination

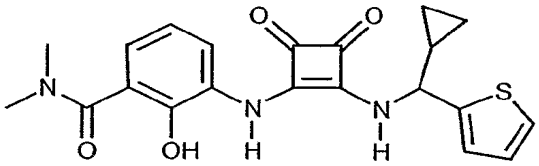
with administering at least one anticancer agent, wherein said anticancer agent is selected from the group consisting of: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids, and synthetics.

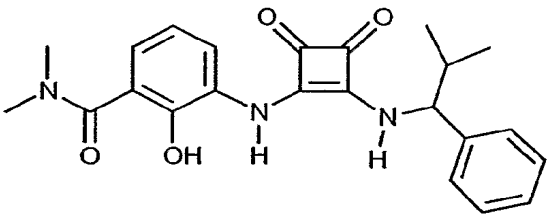
Representative compounds used to treat the chemokine mediated diseases include but are not limited to:

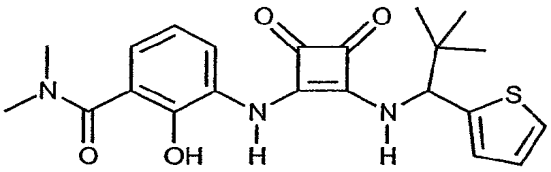


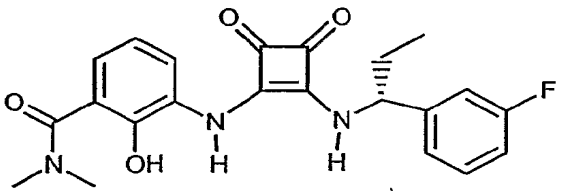


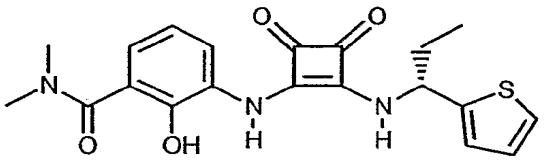


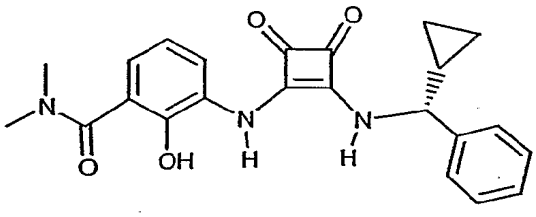


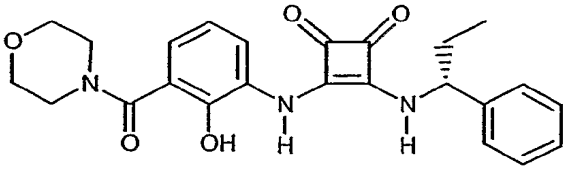


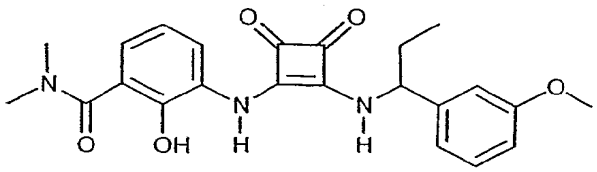


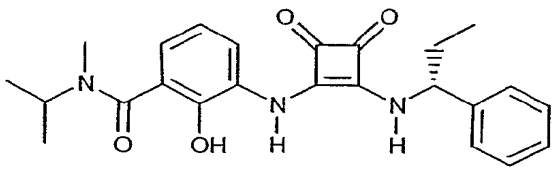


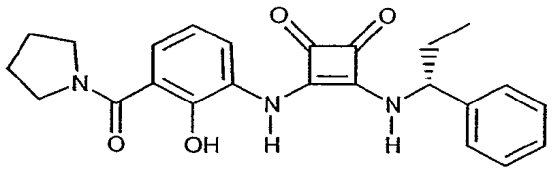


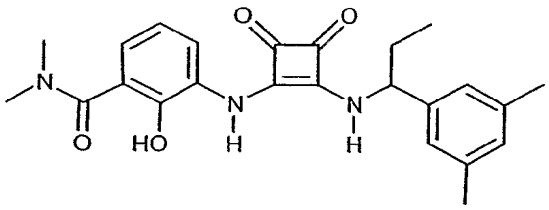


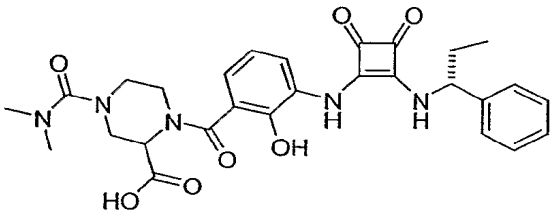


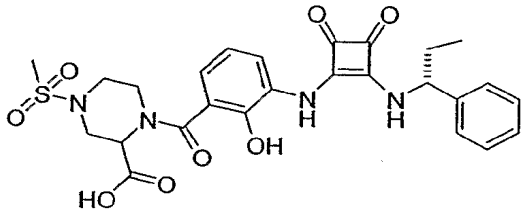


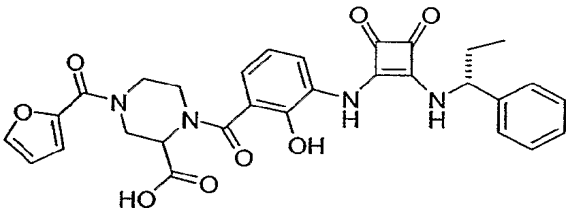


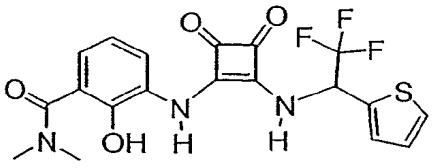


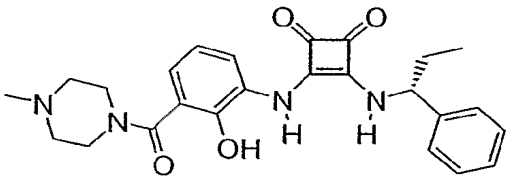


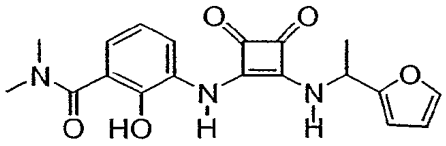


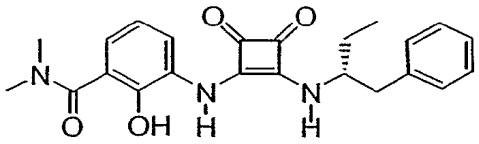


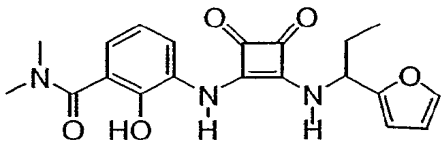


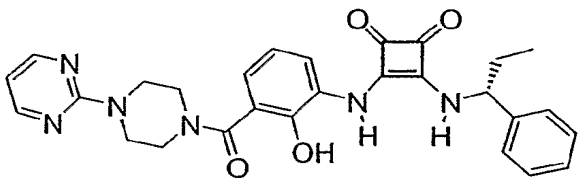


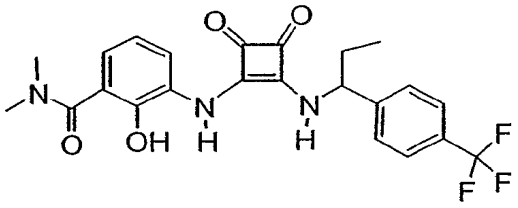


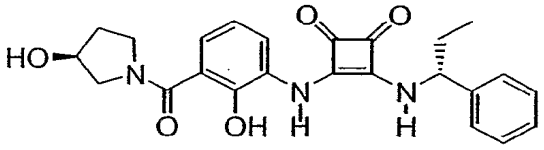


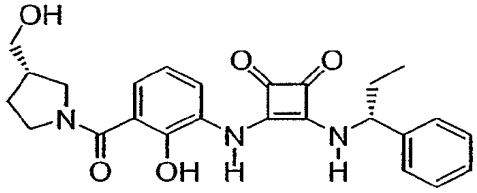


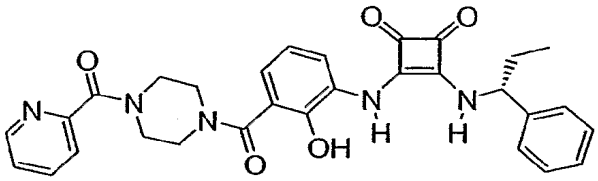


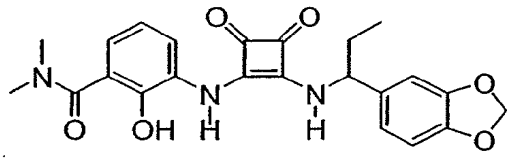


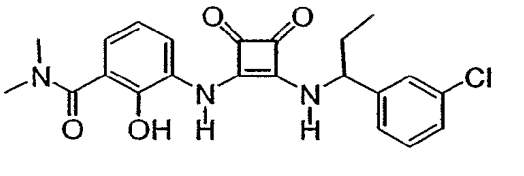


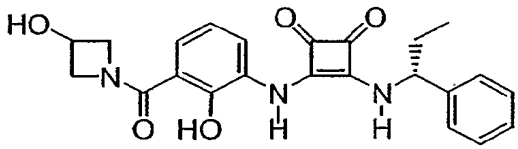


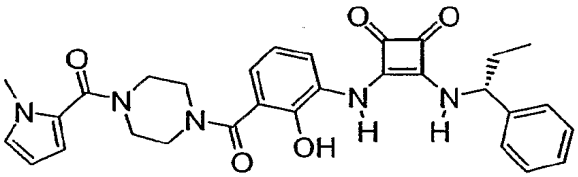


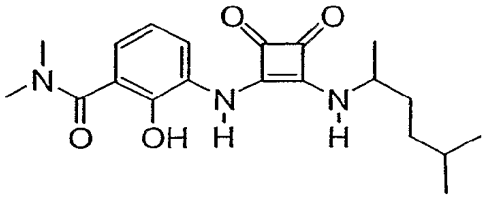


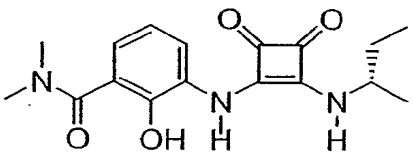


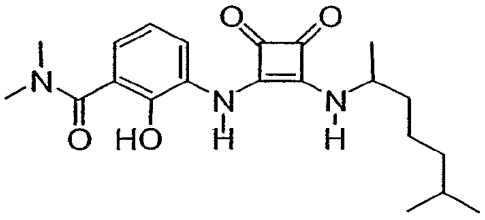


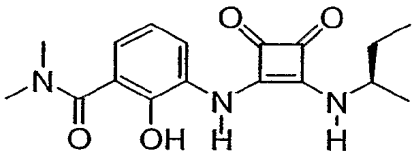


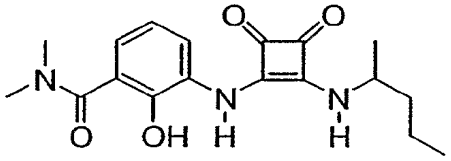


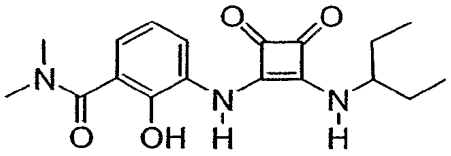


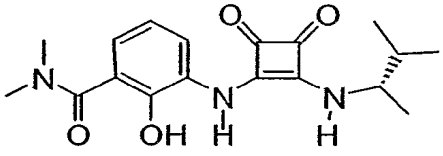


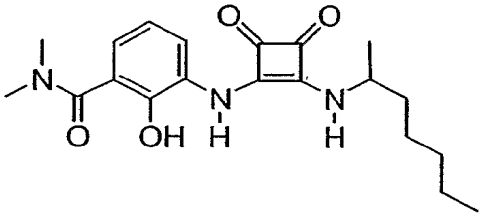


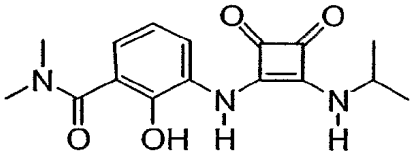


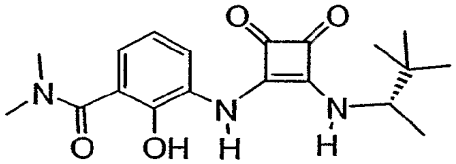


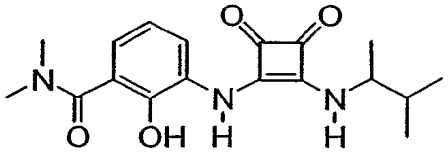


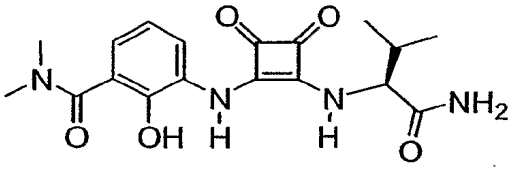


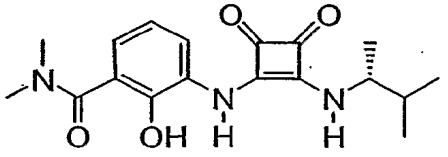


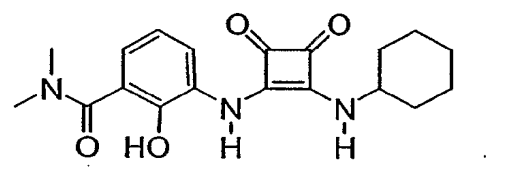


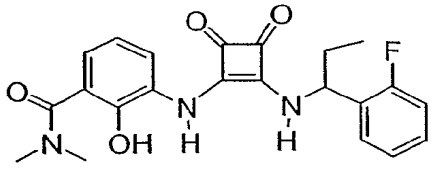


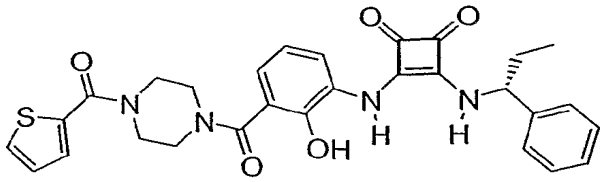


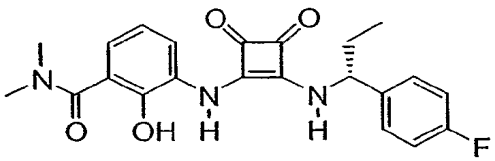


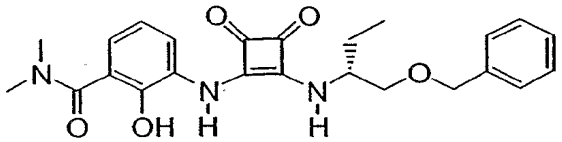


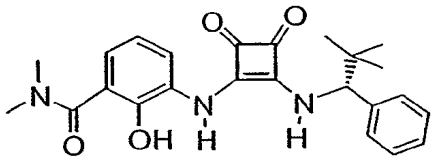


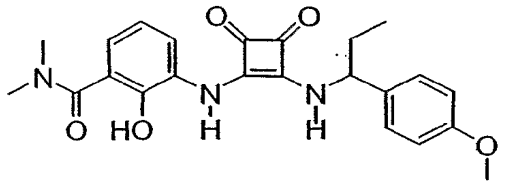


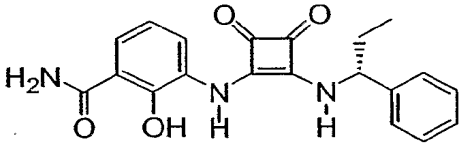


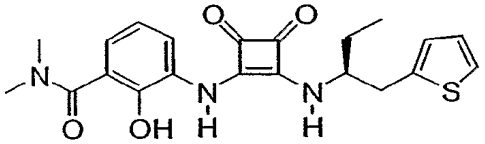


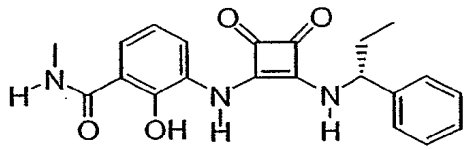


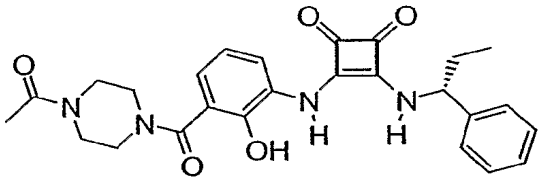


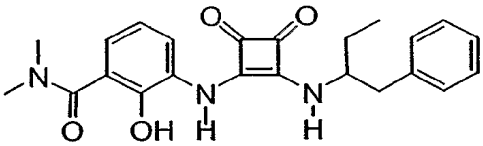


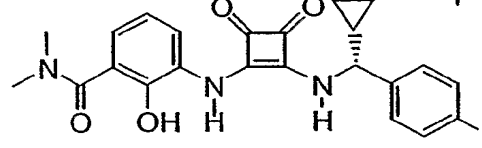


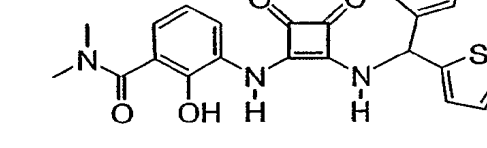


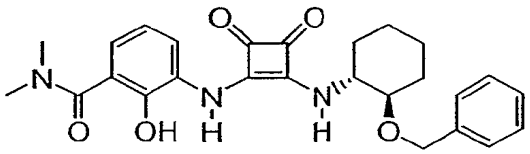


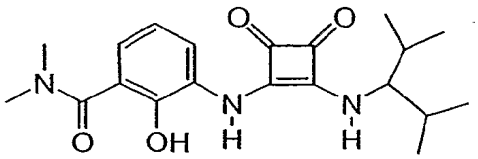


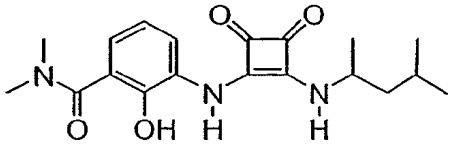


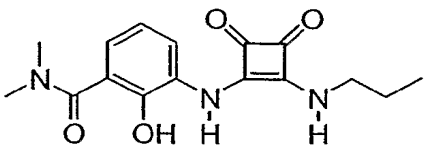


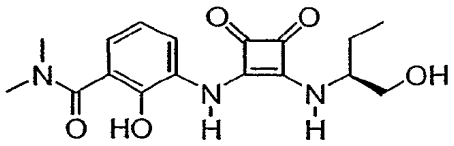


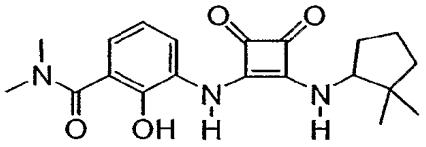


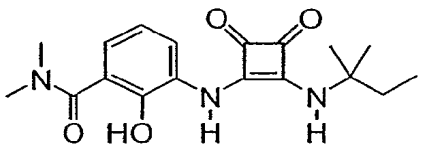


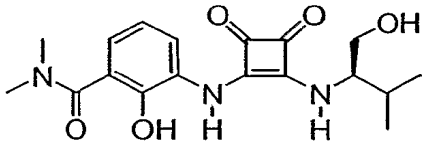


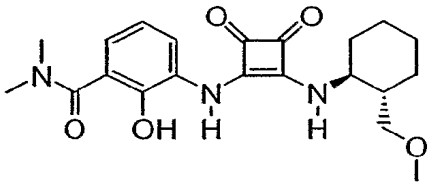


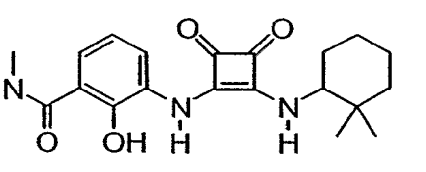


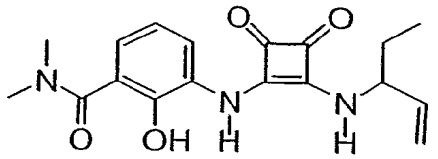


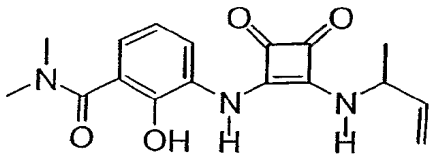


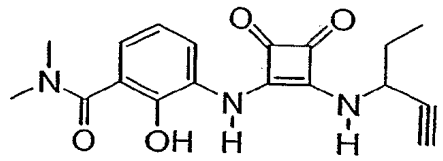


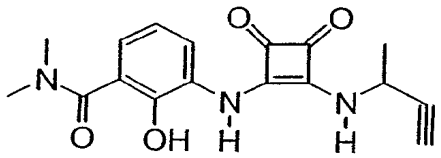


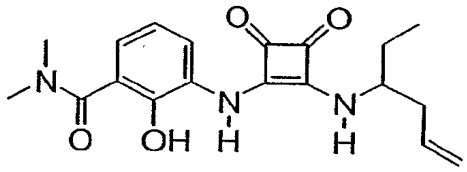


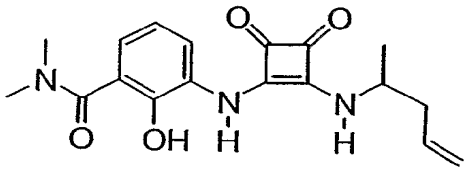


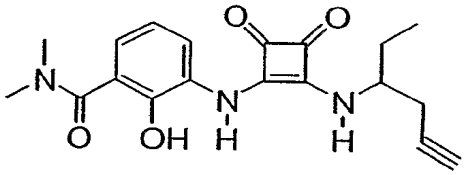


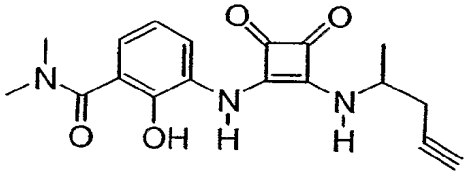


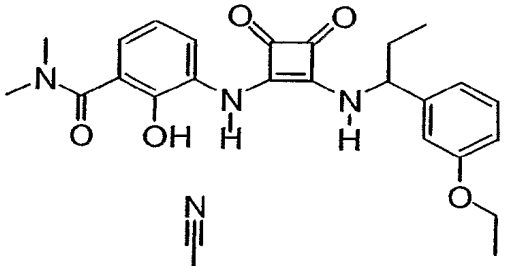


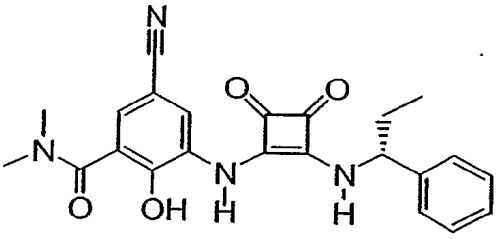


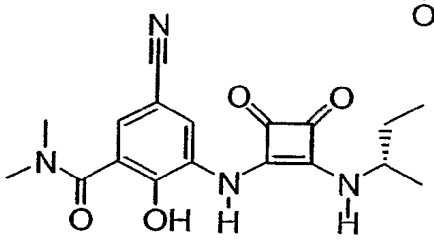


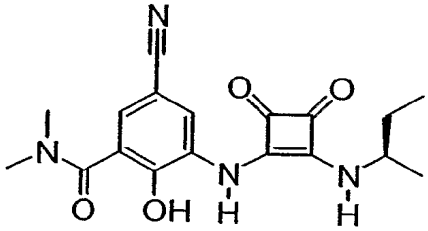


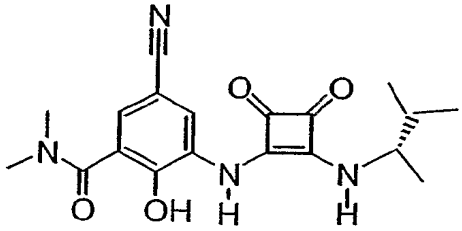


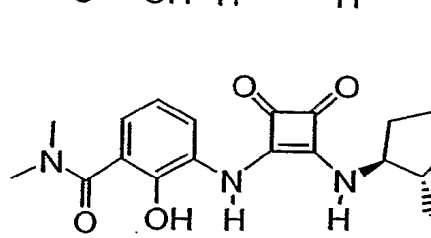


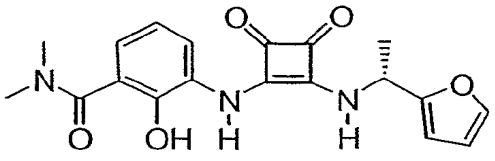


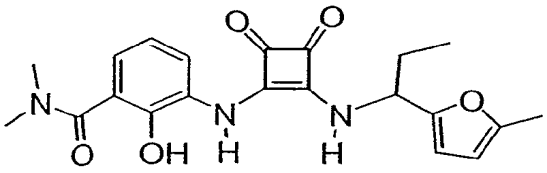


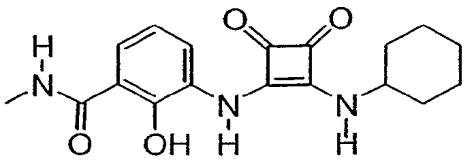


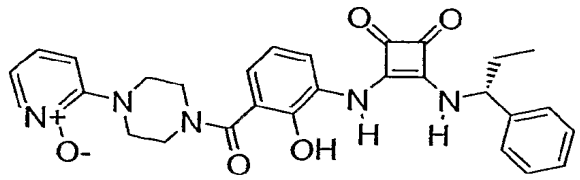


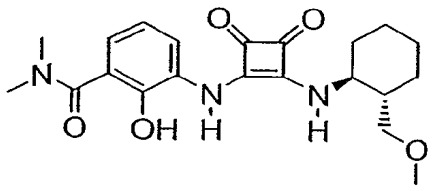


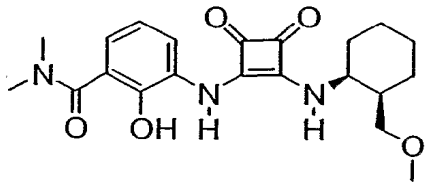


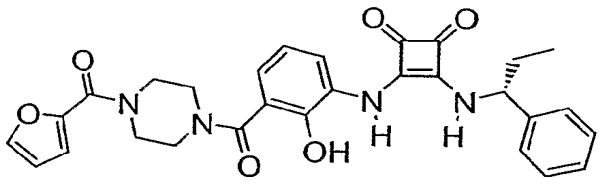


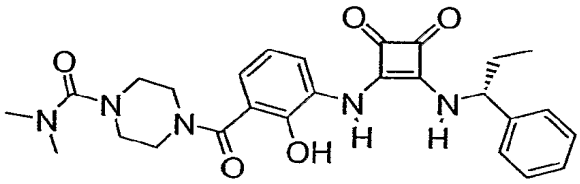


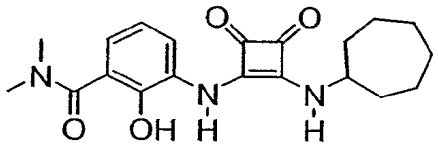


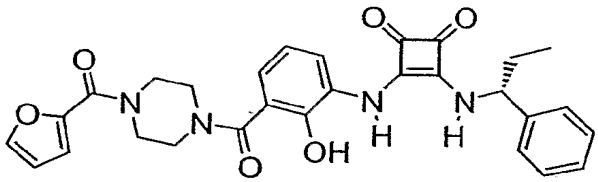


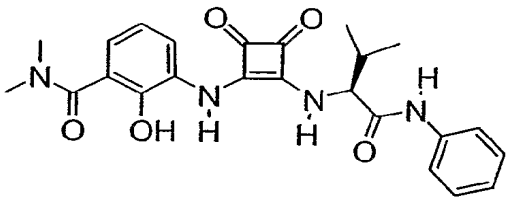


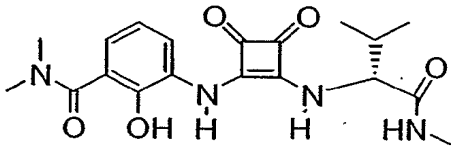


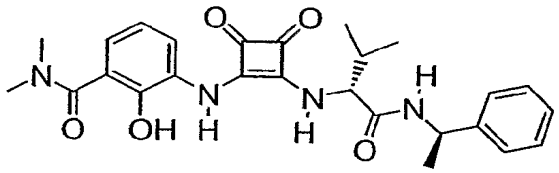


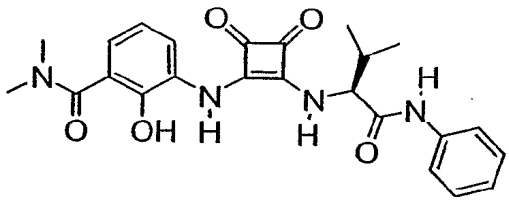


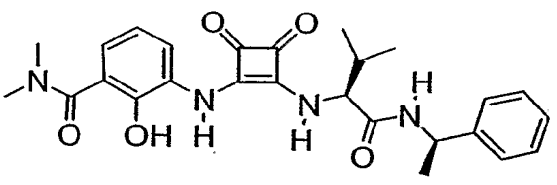


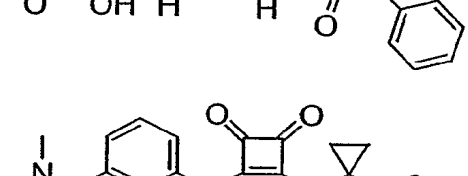


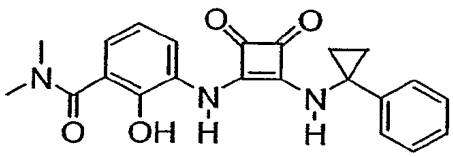


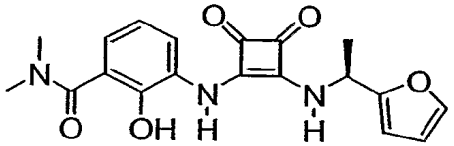


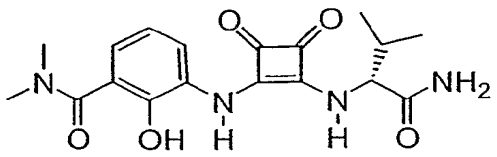


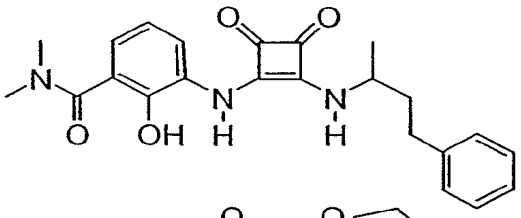


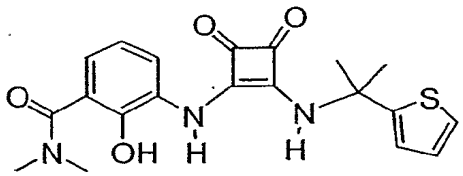


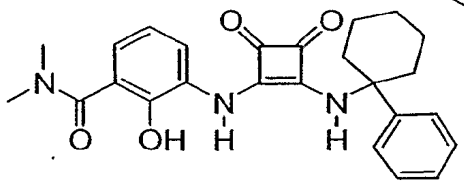


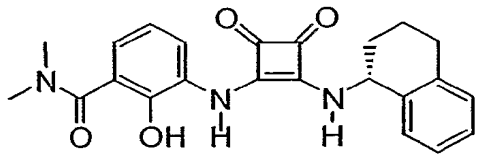


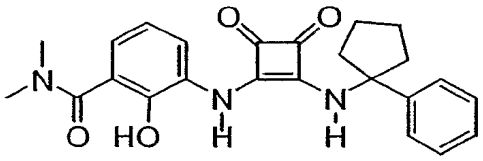


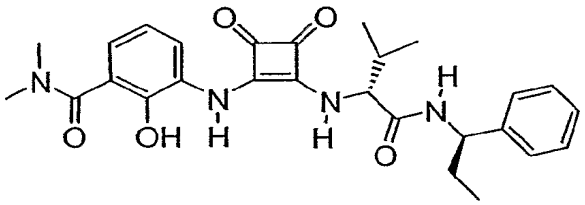


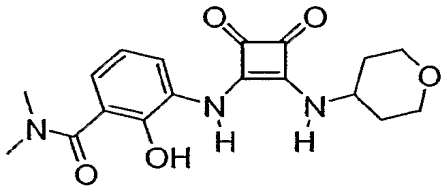


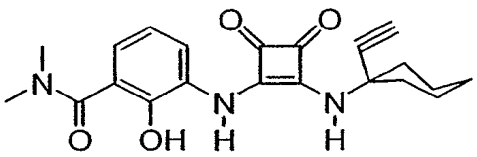


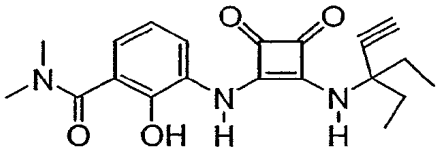


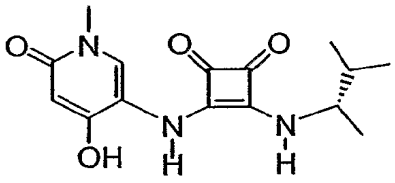


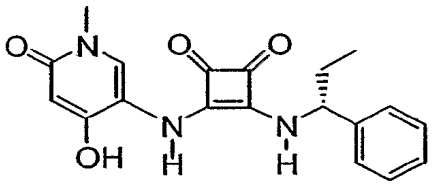


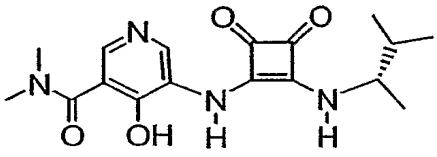


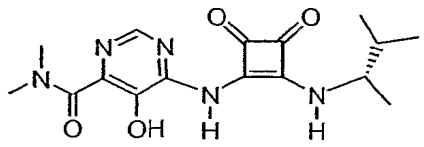


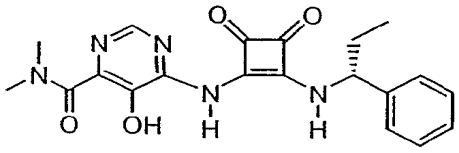


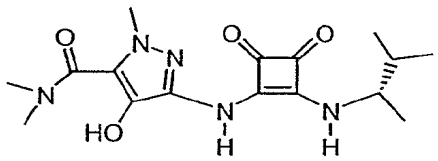


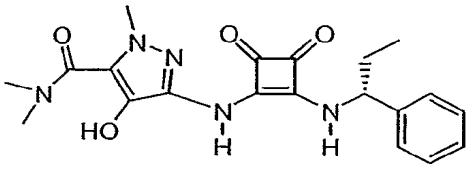


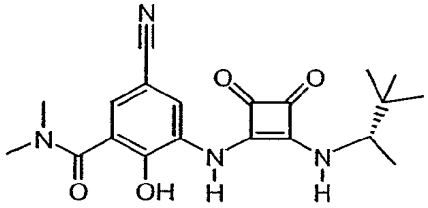


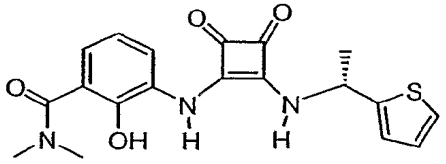


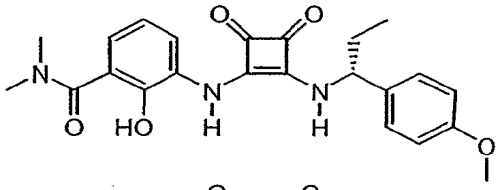


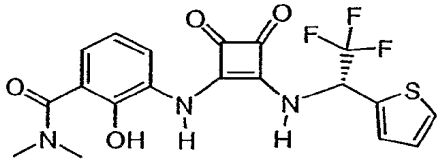


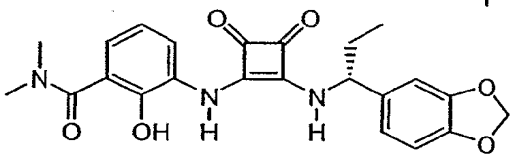


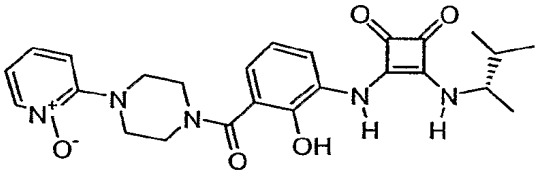


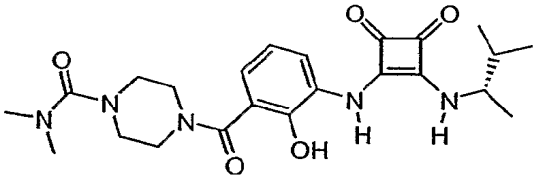


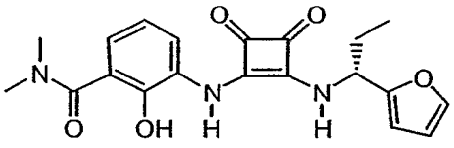


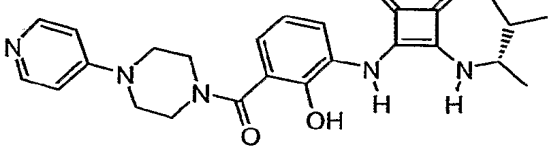


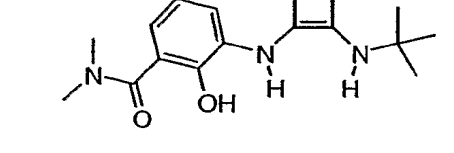


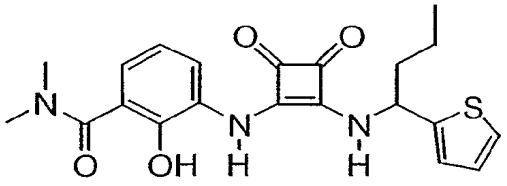


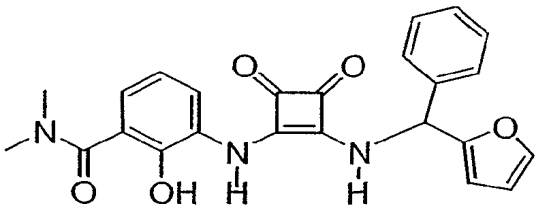


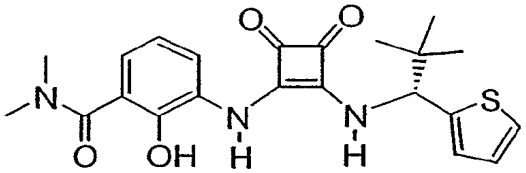


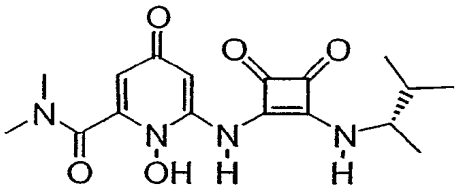


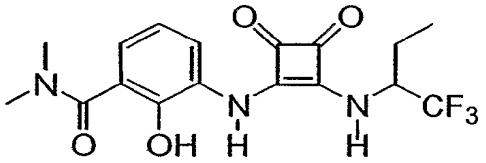


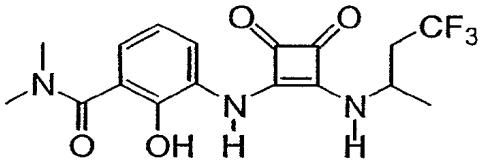


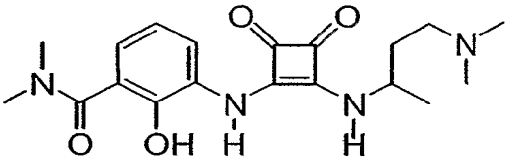


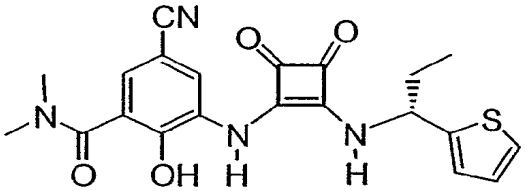


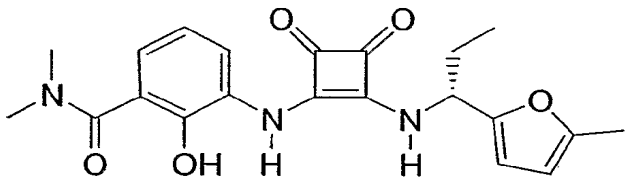


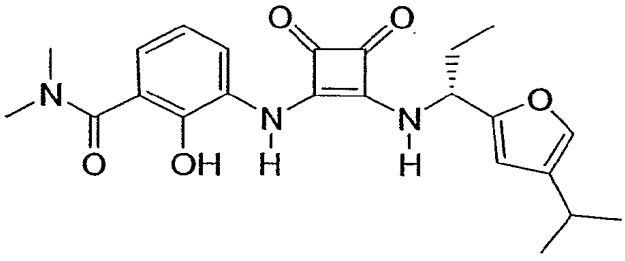


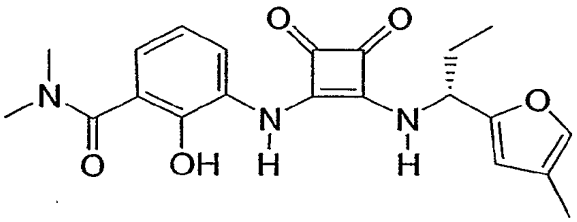


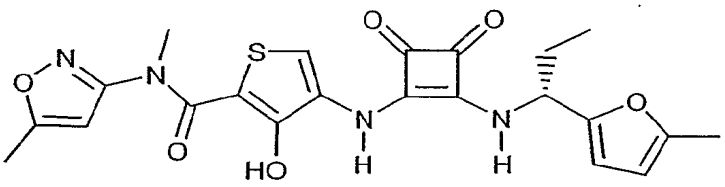


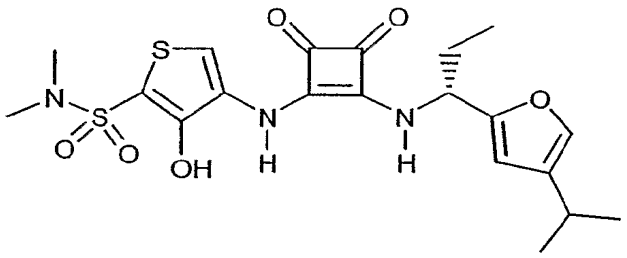


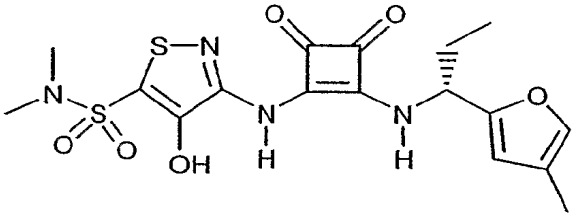


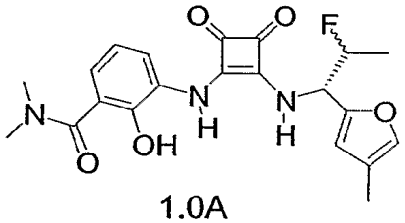




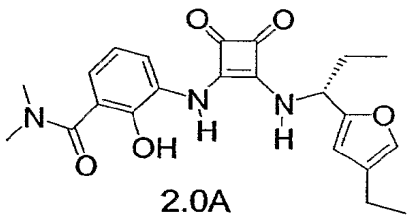




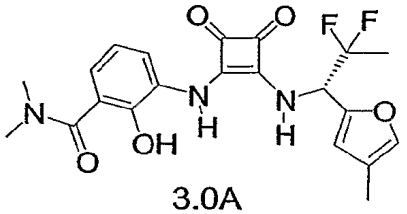




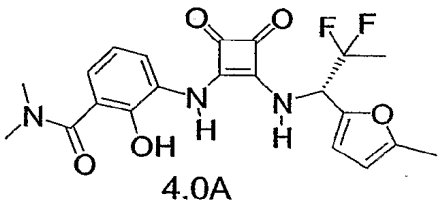
1.0A



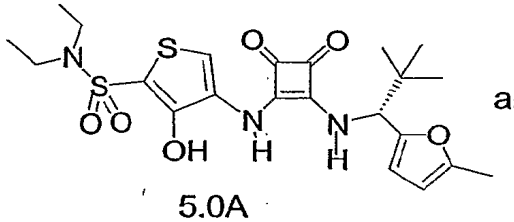
2.0A



3.0A

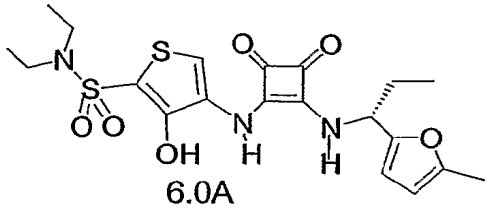


4.0A



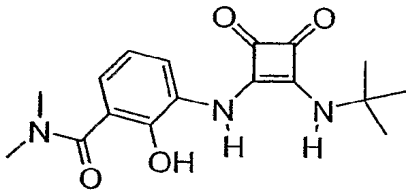
5.0A

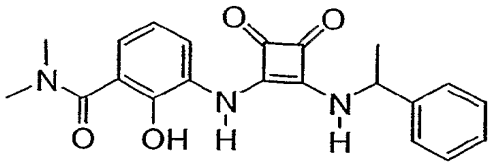
and

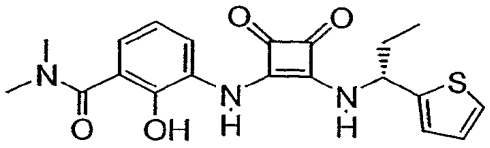


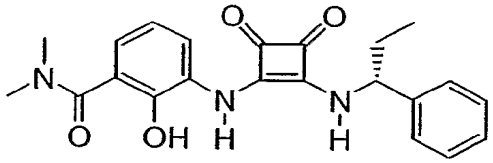
6.0A

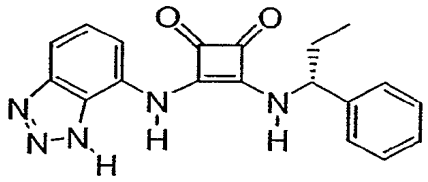
Preferred compounds used to treat the chemokine mediated diseases include but are not limited to:

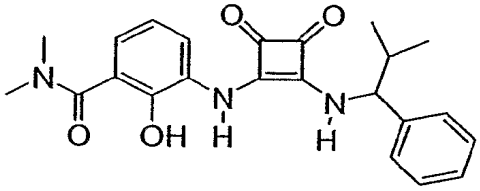


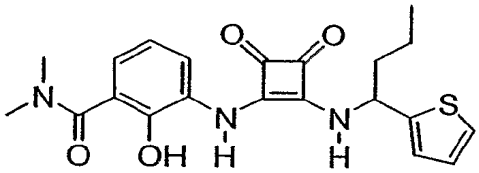


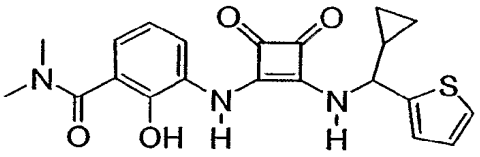


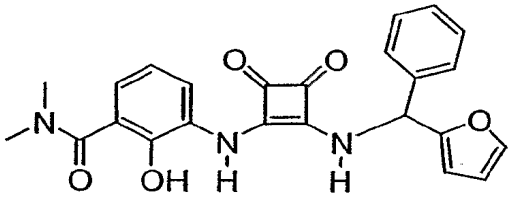


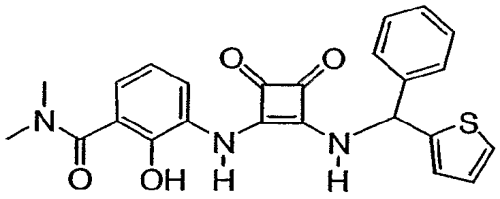


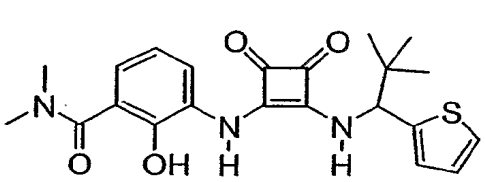


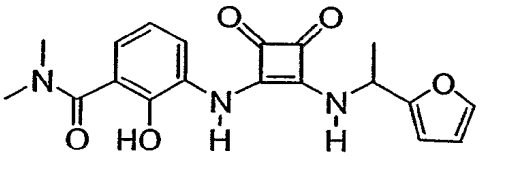


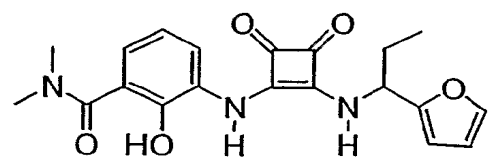


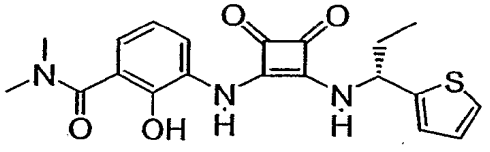












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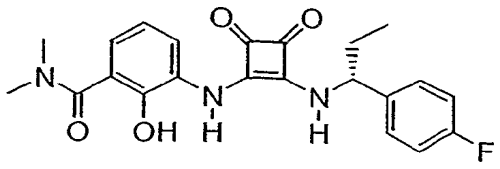
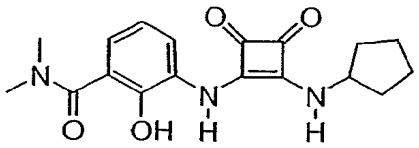
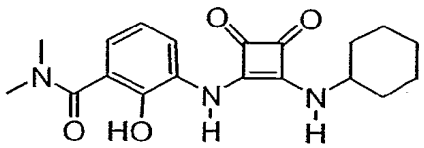
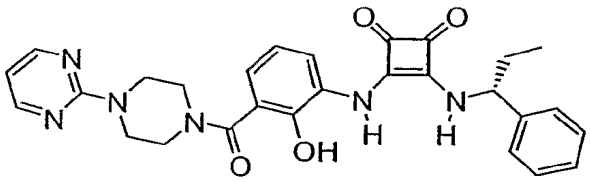
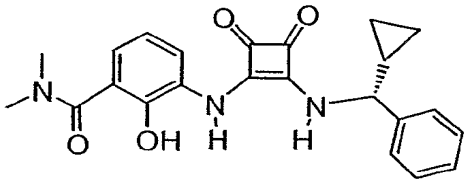
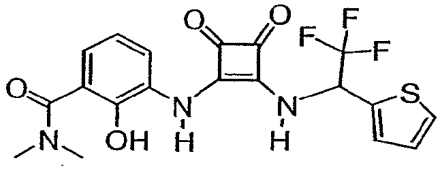


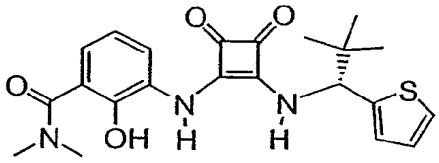


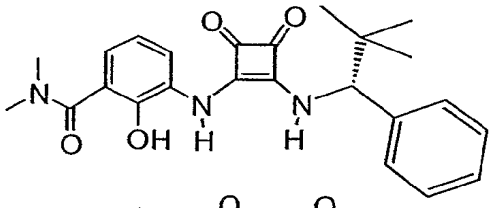


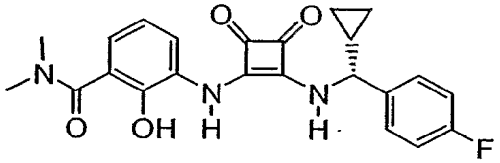


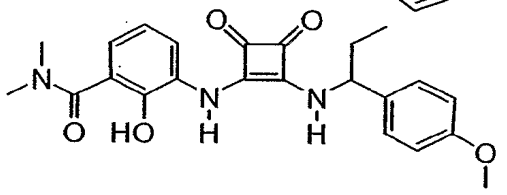


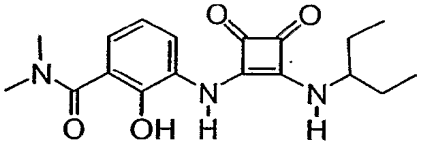


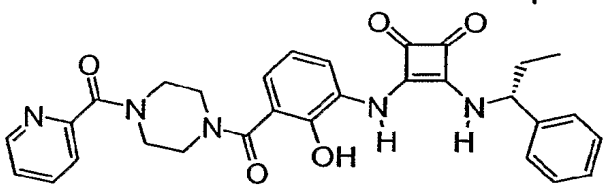


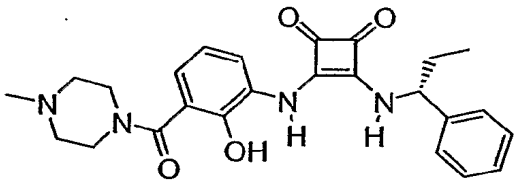


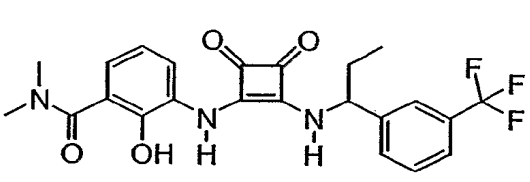


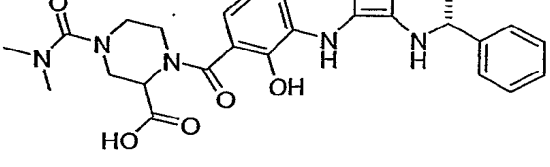


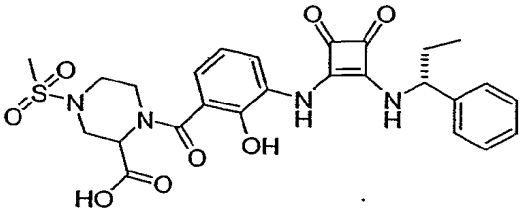


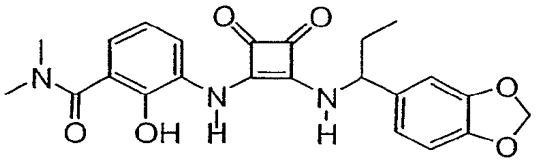


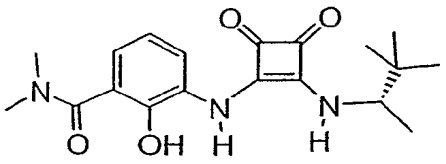


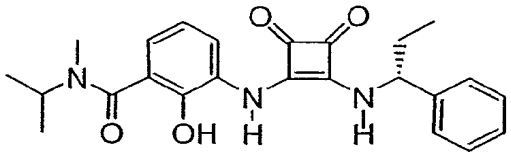


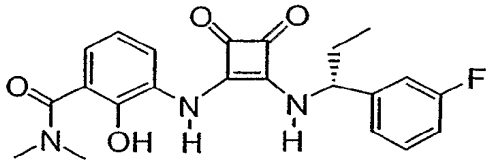


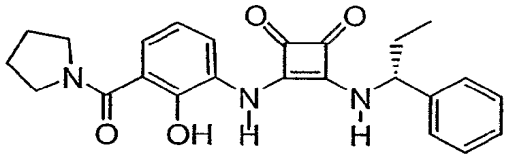


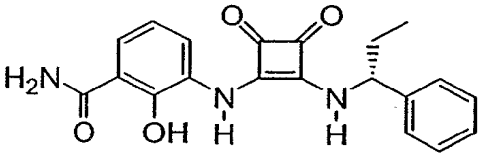


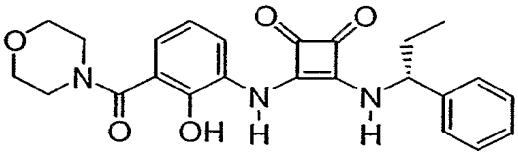


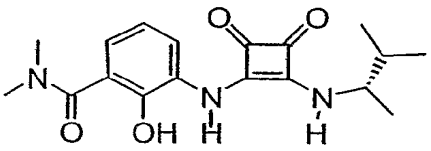


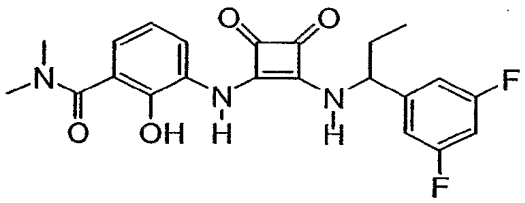


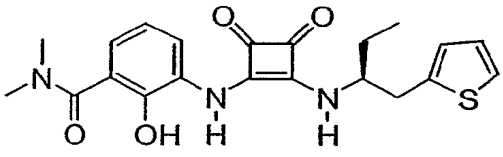


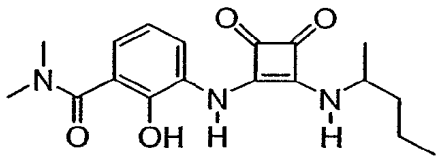


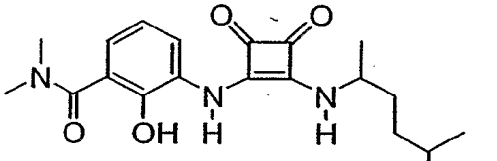


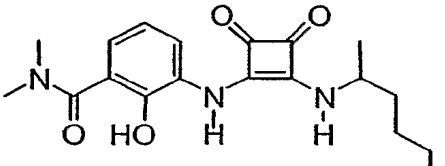


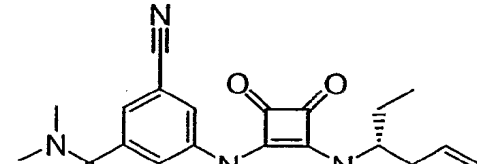


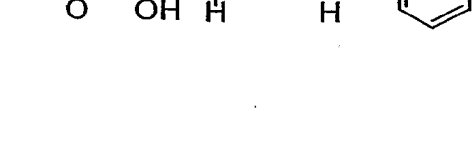


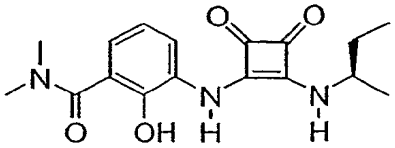


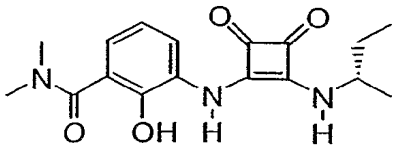


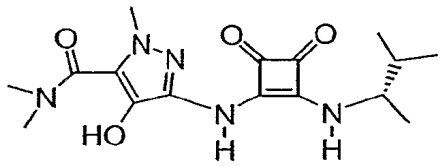


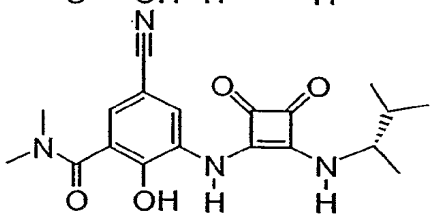


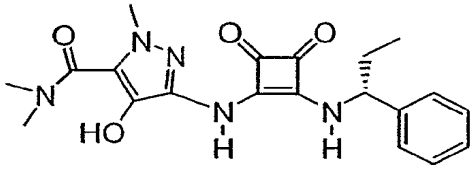


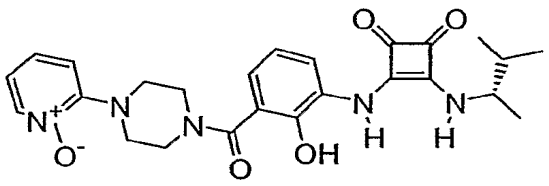


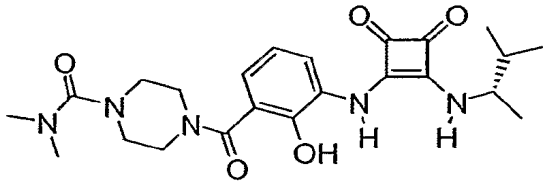


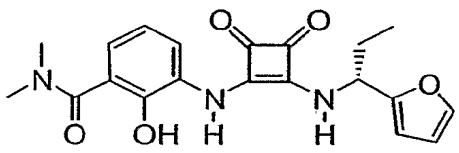


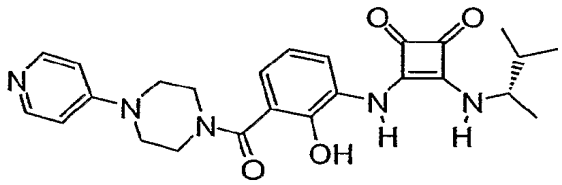


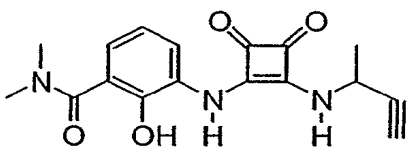


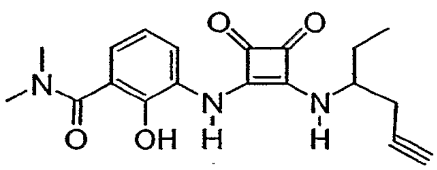


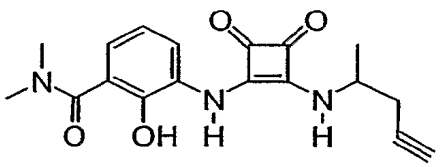


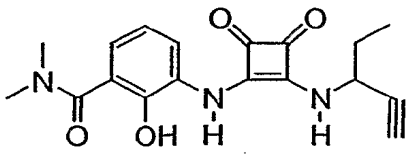


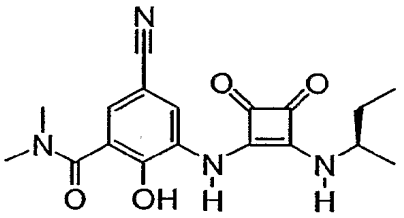


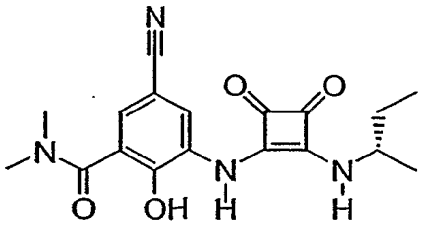


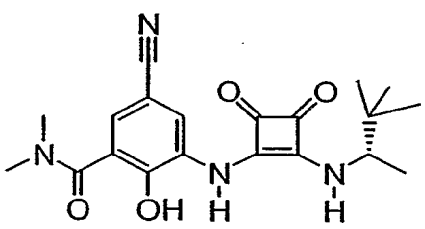


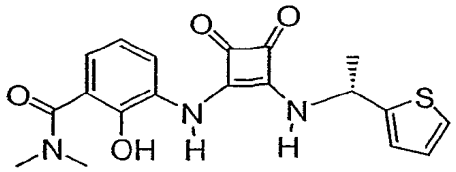


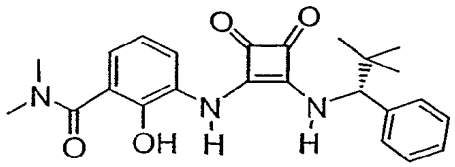


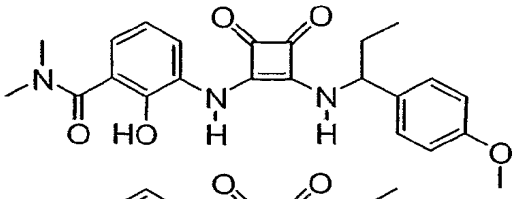


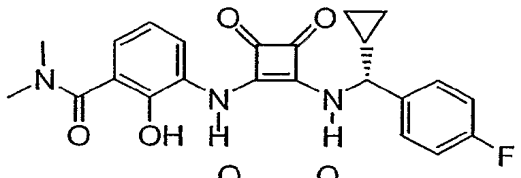


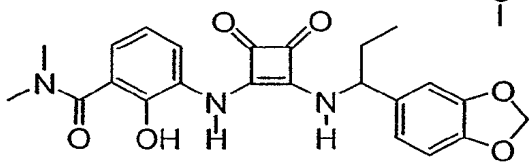


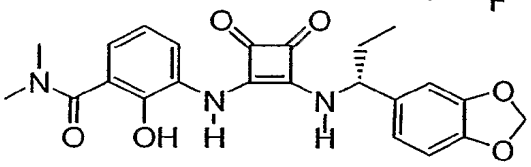


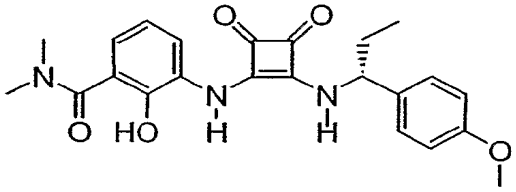


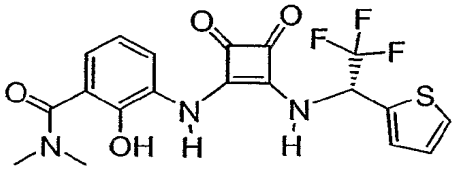


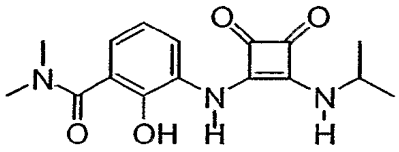


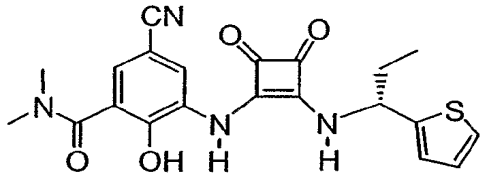


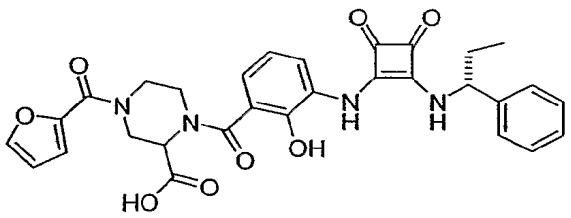


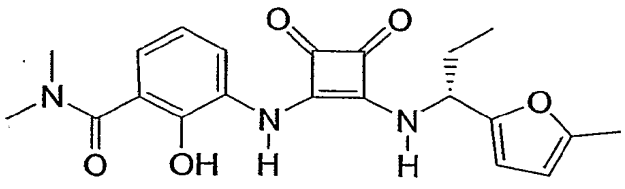


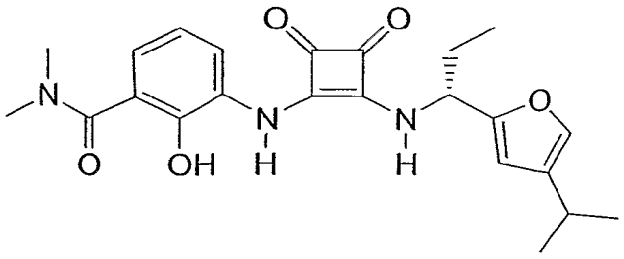


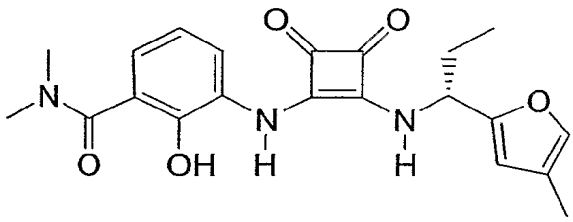


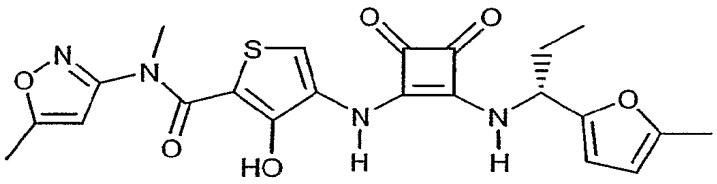


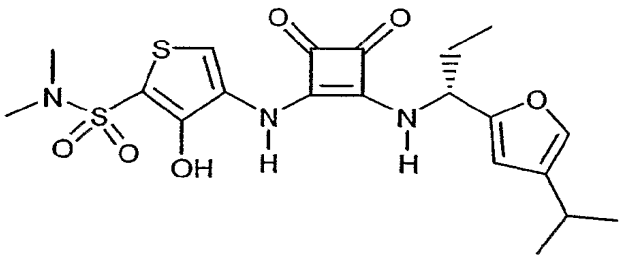


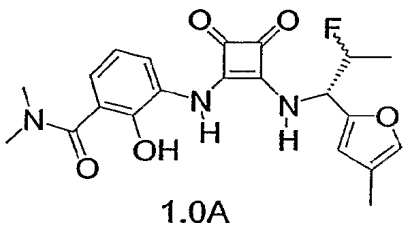




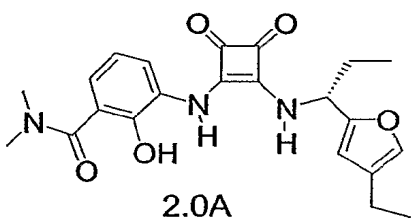




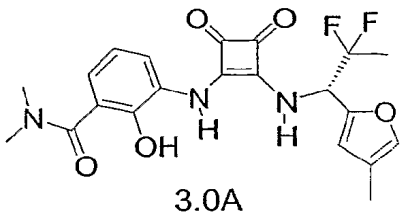




1.0A



2.0A



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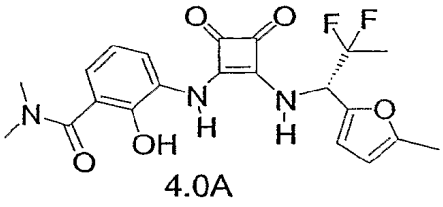

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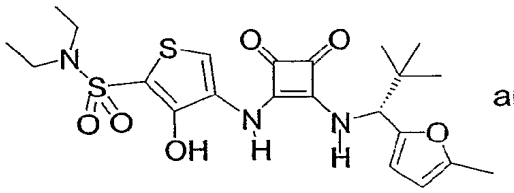
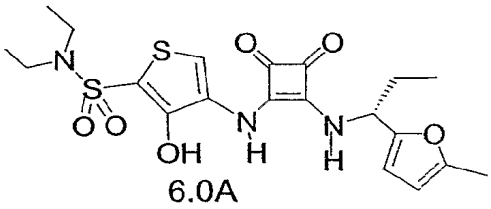


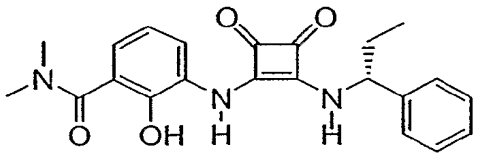
5.0A

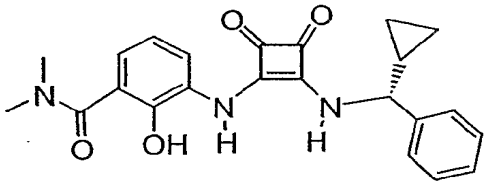
and

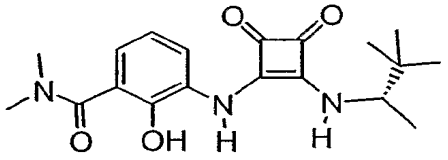


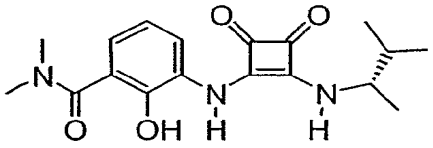
6.0A

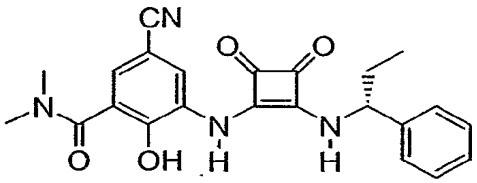
A more preferred group of compounds used to treat the chemokine mediated diseases include but are not limited to

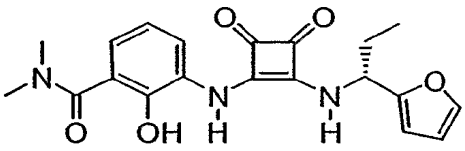


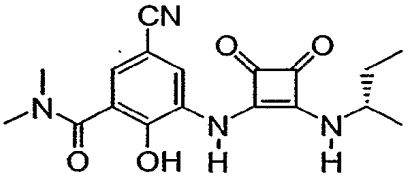


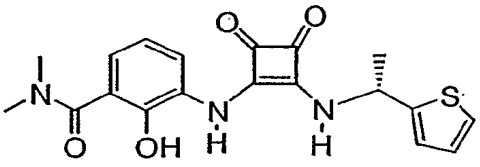


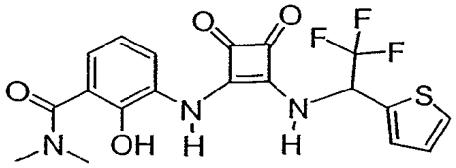


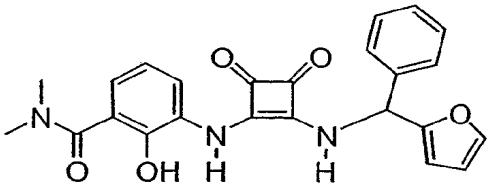


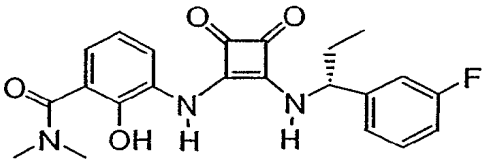


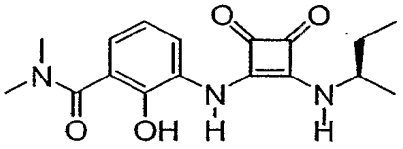


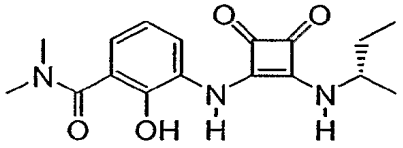


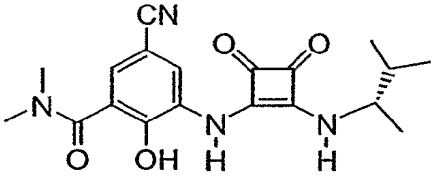


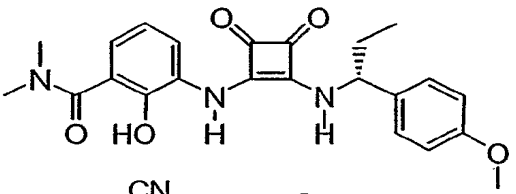


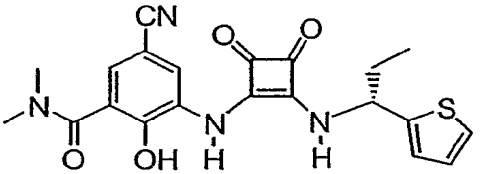


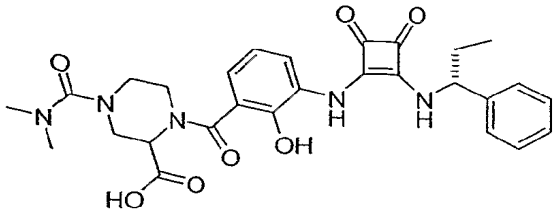


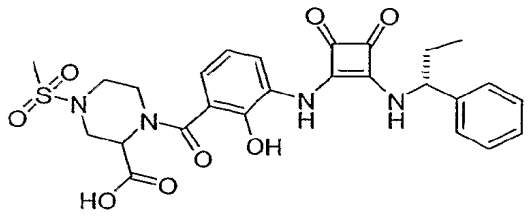


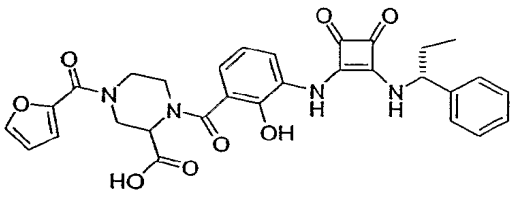












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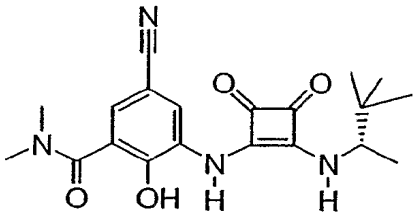

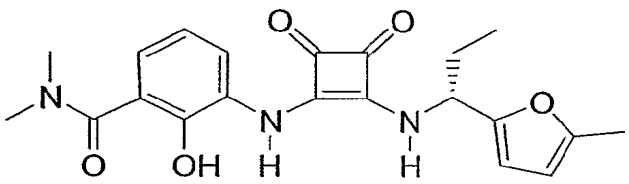

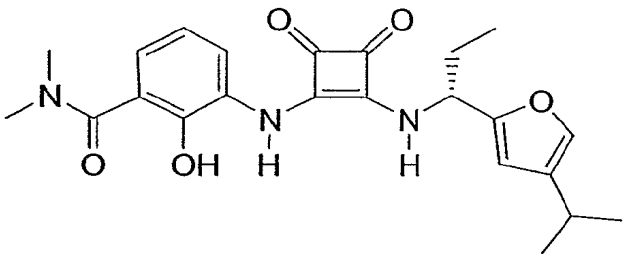

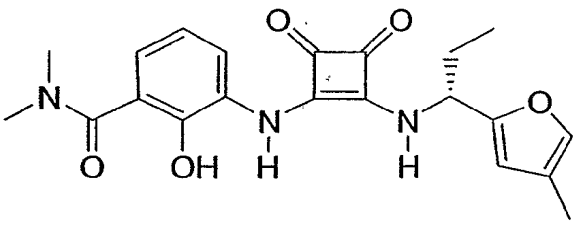

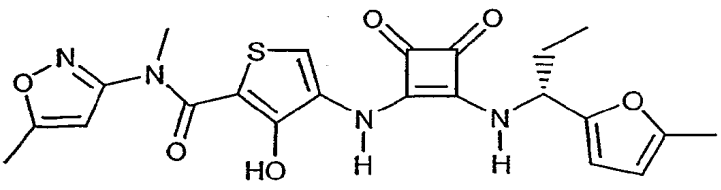

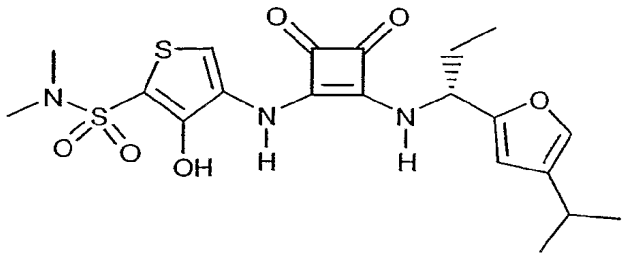

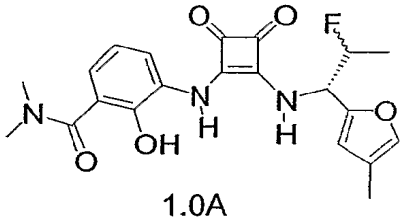

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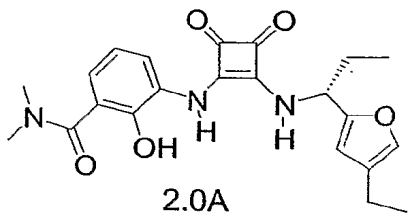

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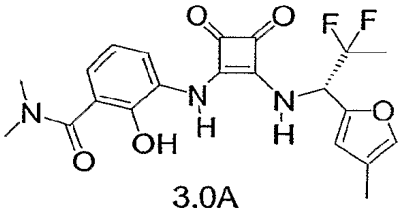

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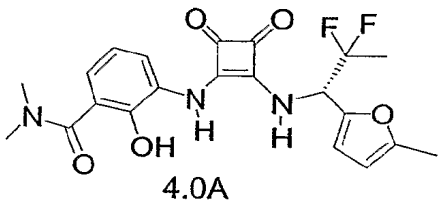

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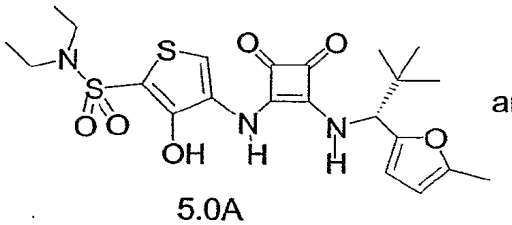
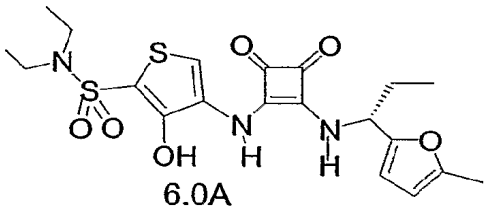


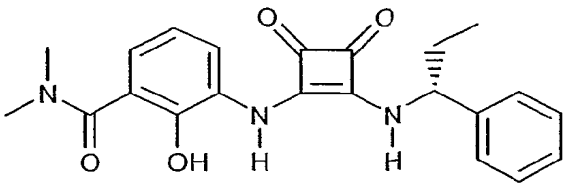
5.0A

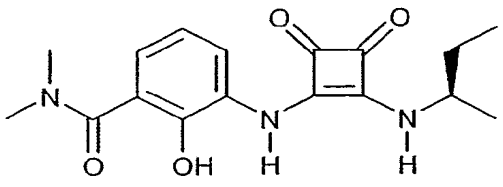
and

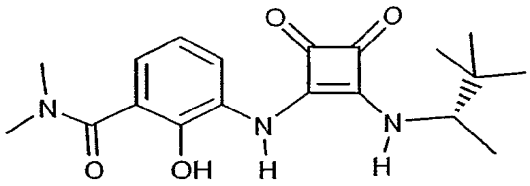


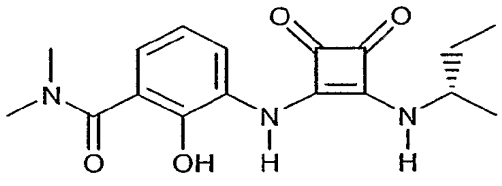
6.0A

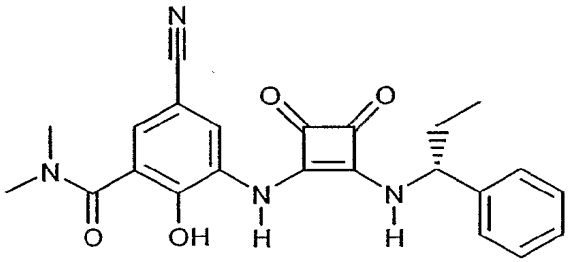
A most preferred group of compounds used to treat the chemokine mediated diseases include but are not limited to

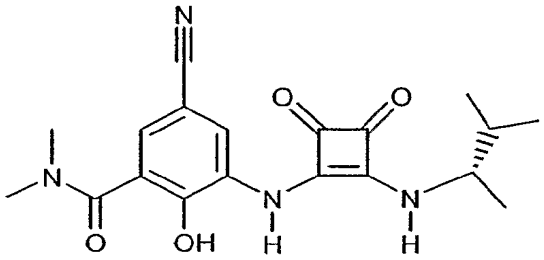


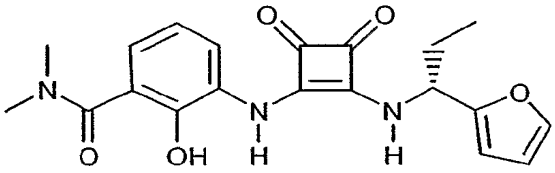


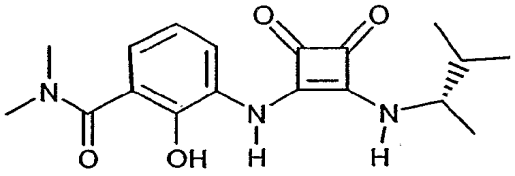


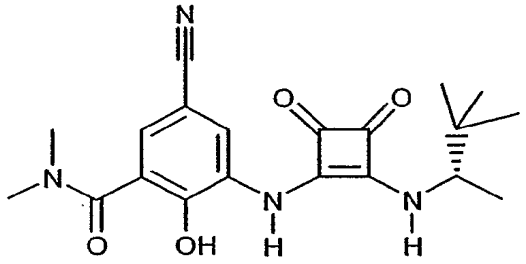


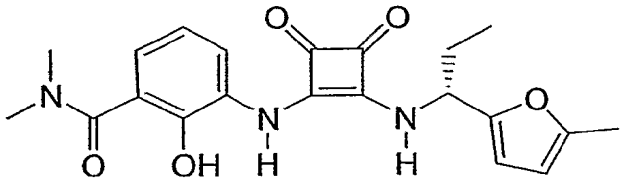


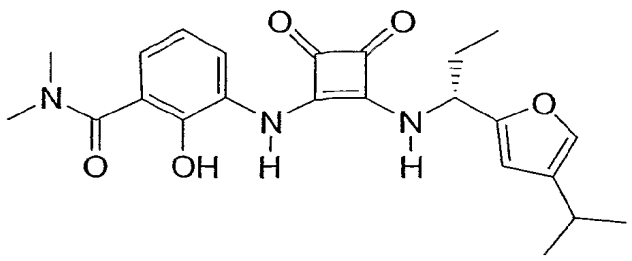


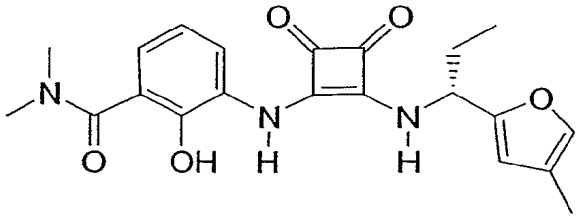


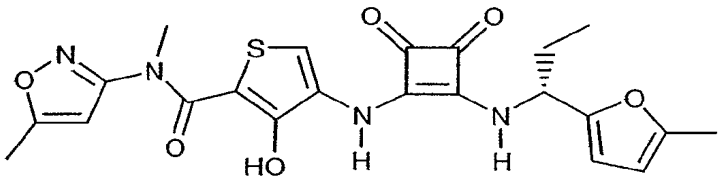


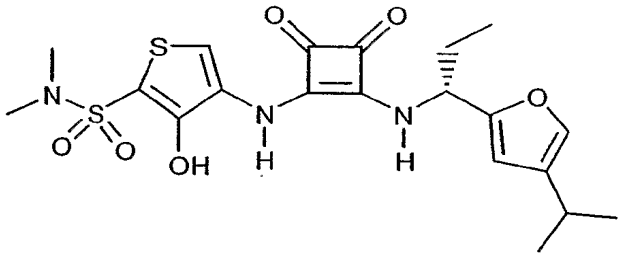


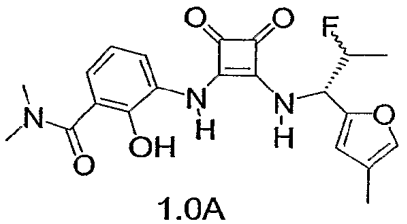




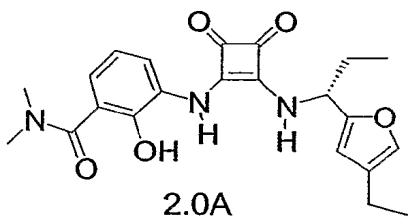




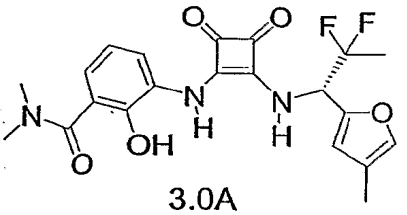




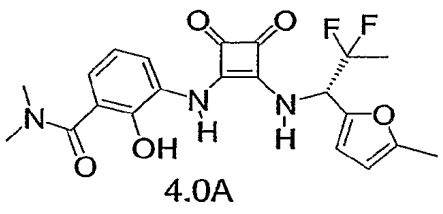
1.0A



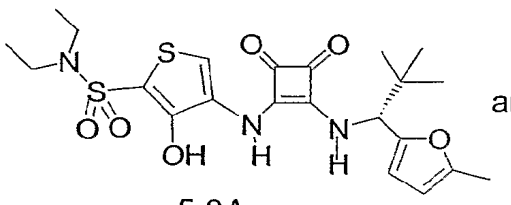
2.0A



3.0A

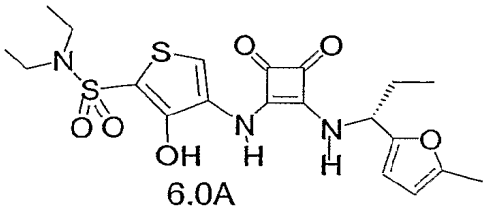


4.0A



5.0A

and



6.0A

Certain compounds of the invention may exist in different stereoisomeric forms (e.g., enantiomers, diastereoisomers and atropisomers). The invention contemplates all such stereoisomers both in pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional methods.

This invention also includes Prodrugs of the compounds of this invention.

Certain compounds will be acidic in nature, e.g. those compounds that possess a carboxyl or phenolic hydroxyl group. These compounds may form pharmaceutically acceptable salts. Examples of such salts may include sodium, potassium, calcium, aluminum, gold and silver salts. Also contemplated are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Certain basic compounds also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the pyrido-nitrogen atoms may form salts with strong acid, while compounds having basic substituents such as amino groups also form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of the invention can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

In an embodiment of the treatment of cancer, a compound selected from the group consisting of compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) is administered in combination with one of the following antineoplastic agents: gemcitabine, paclitaxel (Taxol®), 5-Fluorourcil (5-FU), cyclophosphamide (Cytoxan®), temozolomide, or Vincristine.

In another embodiment, the present invention provides a method of treating cancer, comprising administering, concurrently or sequentially, and effective amount of a compound selected from the group consisting of compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and a microtubule affecting agent e.g., paclitaxel.

Another embodiment of the invention is directed to a method treating cancer, comprising administering to a patient in need thereof, concurrently or sequentially, a therapeutically effective amount of (a) a compound selected from the group consisting of compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and (b) an antineoplastic agent, microtubule affecting agent or anti-angiogenesis agent.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules,

cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal composition can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.01 mg to about 1000 mg, preferably from about 0.01 mg to about 750 mg, more preferably from about 0.01 mg to about 500 mg, and most preferably from about 0.01 mg to about 250 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 0.04 mg/day to about 4000 mg/day, in two to four divided doses.

Classes of compounds that can be used as the chemotherapeutic agent (antineoplastic agent) include: alkylating agents, antimetabolites, natural products and their derivatives, hormones and steroids (including synthetic analogs), and synthetics. Examples of compounds within these classes are given below.

Alkylating agents (including nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes): Uracil mustard, Chlormethine, Cyclophosphamide (Cytoxan®), Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylene-melamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, and Temozolomide.

Antimetabolites (including folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors): Methotrexate, 5-Fluorouracil, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, Pentostatine, and Gemcitabine.

Natural products and their derivatives (including vinca alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins): Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, paclitaxel (paclitaxel is commercially available as Taxol® and is described in more detail below in the subsection entitled "Microtubule Affecting Agents"), Mithramycin, Deoxyco-formycin, Mitomycin-C, L-Asparaginase, Interferons (especially IFN-a), Etoposide, and Teniposide.

Hormones and steroids (including synthetic analogs): 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone

propionate, Testolactone, Megestrolacetate, Tamoxifen, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, Zoladex.

Synthetics (including inorganic complexes such as platinum coordination complexes): Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, and Hexamethylmelamine.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 2002 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

As used herein, a microtubule affecting agent is a compound that interferes with cellular mitosis, *i.e.,* having an anti-mitotic effect, by affecting microtubule formation and/or action. Such agents can be, for instance, microtubule stabilizing agents or agents that disrupt microtubule formation.

Microtubule affecting agents useful in the invention are well known to those of skill in the art and include, but are not limited to allocolchicine (NSC 406042), Halichondrin B (NSC 609395), colchicine (NSC 757), colchicine derivatives (e.g., NSC 33410), dolastatin 10 (NSC 376128), maytansine (NSC 153858), rhizoxin (NSC 332598), paclitaxel (Taxol®, NSC 125973), Taxol® derivatives (*e.g.,* derivatives (*e.g.,* NSC 608832), thiocolchicine (NSC 361792), trityl cysteine (NSC 83265), vinblastine sulfate (NSC 49842), vincristine sulfate (NSC 67574), epothilone A, epothilone, and discodermolide (*see* Service, (1996) *Science*, 274:2009) estramustine, nocodazole, MAP4, and the like. Examples of such agents are also described in the scientific and patent literature, see, *e.g.,* Bulinski (1997) *J. Cell Sci.* 110:3055-3064; Panda (1997) *Proc. Natl. Acad. Sci.* USA 94:10560-10564; Muhlradt (1997) Cancer Res. 57:3344-3346; Nicolaou (1997) *Nature* 387:268-272; Vasquez (1997) *Mol. Biol. Cell.* 8:973-985; Panda (1996) *J. Biol. Chem.* 271:29807-29812.

Particularly preferred agents are compounds with paclitaxel-like activity. These include, but are not limited to paclitaxel and paclitaxel derivatives (paclitaxel-like

compounds) and analogues. Paclitaxel and its derivatives are available commercially. In addition, methods of making paclitaxel and paclitaxel derivatives and analogues are well known to those of skill in the art (*see, e.g.,* U.S. Patent Nos: 5,569,729; 5,565,478; 5,530,020; 5,527,924; 5,508,447; 5,489,589; 5,488,116; 5,484,809; 5,478,854; 5,478,736; 5,475,120; 5,468,769; 5,461,169; 5,440,057; 5,422,364; 5,411,984; 5,405,972; and 5,296,506).

More specifically, the term "paclitaxel" as used herein refers to the drug commercially available as Taxol® (NSC number: 125973). Taxol® inhibits eukaryotic cell replication by enhancing polymerization of tubulin moieties into stabilized microtubule bundles that are unable to reorganize into the proper structures for mitosis. Of the many available chemotherapeutic drugs, paclitaxel has generated interest because of its efficacy in clinical trials against drug-refractory tumors, including ovarian and mammary gland tumors (Hawkins (1992) *Oncology*, 6: 17-23, Horwitz (1992) *Trends Pharmacol. Sci.* 13: 134-146, Rowinsky (1990) *J. Natl. Canc. Inst.* 82: 1247-1259).

Additional microtubule affecting agents can be assessed using one of many such assays known in the art, *e.g.,* a semiautomated assay which measures the tubulin-polymerizing activity of paclitaxel analogs in combination with a cellular assay to measure the potential of these compounds to block cells in mitosis (see *Lopes* (1997) *Cancer Chemother. Pharmacol.* 41:37-47).

Generally, activity of a test compound is determined by contacting a cell with that compound and determining whether or not the cell cycle is disrupted, in particular, through the inhibition of a mitotic event. Such inhibition may be mediated by disruption of the mitotic apparatus, *e.g.,* disruption of normal spindle formation. Cells in which mitosis is interrupted may be characterized by altered morphology (*e.g.,* microtubule compaction, increased chromosome number, etc.).

Compounds with possible tubulin polymerization activity can be screened *in vitro*. In a preferred embodiment, the compounds are screened against cultured WR21 cells (derived from line 69-2 wap-ras mice) for inhibition of proliferation and/or for altered cellular morphology, in particular for microtubule compaction. *In vivo* screening of positive-testing compounds can then be performed using nude mice bearing the WR21 tumor cells. Detailed protocols for this screening method are described by Porter (1995) *Lab. Anim. Sci.,* 45(2):145-150.

Other methods of screening compounds for desired activity are well known to those of skill in the art. Typically such assays involve assays for inhibition of microtubule assembly and/or disassembly. Assays for microtubule assembly are described, for example, by Gaskin *et al.* (1974) *J. Molec. Biol.*, 89: 737-758. U.S. Patent No. 5,569,720 also provides *in vitro* and *in vivo* assays for compounds with paclitaxel-like activity.

Methods for the safe and effective administration of the above-mentioned microtubule affecting agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, NJ 07645-1742, USA); the disclosure of which is incorporated herein by reference thereto.

The amount and frequency of administration of the compounds of formulas IA, IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agents and/or radiation therapy will be regulated according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease being treated. A dosage regimen of the compounds of formulas IA, IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) can be oral administration of from 10 mg to 2000 mg/day, preferably 10 to 1000 mg/day, more preferably 50 to 600 mg/day, in two to four (preferably two) divided doses, to block tumor growth. Intermittant therapy (*e.g.*, one week out of three weeks or three out of four weeks) may also be used.

The chemotherapeutic agent and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g.,

dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or radiation) on the patient, and in view of the observed responses of the disease to the administered therapeutic agents.

Embodiments of this invention are directed to methods of treatment wherein a compounds of the formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) are administered concurrently or sequentially with a chemotherapeutic agent and/or radiation. Thus, it is not necessary that, for example, the chemotherapeutic agent and said compounds, or the radiation and said compounds, should be administered simultaneously or essentially simultaneously. The advantage of a simultaneous or essentially simultaneous administration is well within the determination of the skilled clinician.

Also, in general, the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agent, do not have to be administered in the same pharmaceutical composition, and may, because of different physical and chemical characteristics, have to be administered by different routes. For example, the compounds formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) may be administered orally to generate and maintain good blood levels thereof, while the chemotherapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician .

The particular choice of a compound formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said

compounds), and chemotherapeutic agent and/or radiation will depend upon the diagnosis of the attending physicians and their judgement of the condition of the patient and the appropriate treatment protocol.

The compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and chemotherapeutic agent and/or radiation may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the patient, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds).

If the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agent and/or radiation are not administered simultaneously or essentially simultaneously, then the initial order of administration of the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), and the chemotherapeutic agent and/or radiation, may not be important. Thus, the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) may be administered first, followed by the administration of the chemotherapeutic agent and/or radiation; or the chemo-therapeutic agent and/or radiation may be administered first, followed by the administration of the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds). This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the

number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the patient.

For example, the chemotherapeutic agent and/or radiation may be administered first, especially if it is a cytotoxic agent, and then the treatment continued with the administration of the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds) followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete.

Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a component (therapeutic agent--*i.e.*, the compounds of formulas IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 (or a pharmaceutically acceptable salt or solvate of said compounds), chemotherapeutic agent or radiation) of the treatment according to the individual patient's needs, as the treatment proceeds.

The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the patient as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radio-logical studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

BIOLOGICAL EXAMPLES

The compounds of the present invention are useful in the treatment of CXC-chemokine mediated conditions and diseases. This utility is manifested in their ability to inhibit IL-8 and GRO-α chemokine as demonstrated by the following *in vitro* assays.

Receptor Binding Assays:

CXCR1 SPA Assay

For each well of a 96 well plate, a reaction mixture of 10 μg hCXCR1-CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μl was prepared in CXCR1 assay buffer (25 mM HEPES, pH 7.8, 2 mM $CaCl_2$, 1mM $MgCl_2$, 125 mM NaCl, 0.1% BSA) (Sigma). A 0.4 nM stock of ligand, [125I]-IL-8 (NEN) was prepared in the CXCR1 assay buffer. 20X stock solutions of test compounds were prepared in DMSO (Sigma). A 6 X stock solution of IL-8 (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (PerkinElmer) as follows: 10 μl test compound or DMSO, 40 μl CXCR1 assay buffer or IL-8 stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0.1 nM). The assay plates were shaken for 5 minutes on plate shaker, then incubated for 8 hours before cpm/well were determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of Total binding-NSB (250 nM IL-8) was determined for IC50 values. Compounds of this invention had an IC_{50} of <20μM. The most preferred compounds had a K_i within the range of 3nM to 1120nM.

CXCR2 SPA Assay

For each well of a 96 well plate, a reaction mixture of 4 μg hCXCR2-CHO overexpressing membranes (Biosignal) and 200 μg/well WGA-SPA beads (Amersham) in 100 μl was prepared in CXCR2 assay buffer (25 mM HEPES, pH 7.4, 2 mM $CaCl_2$, 1mM $MgCl_2$). A 0.4 nM stock of ligand, [125I]-IL-8 (NEN), was prepared in the CXCR2 assay buffer. 20X stock solutions of test compounds were prepared in DMSO (Sigma). A 6 X stock solution of GRO-α (R&D) was prepared in CXCR2 assay buffer. The above solutions were added to a 96-well assay plate (PerkinElmer or Corning) as follows: 10 μl test compound or DMSO, 40 ul CXCR2 assay buffer or GRO- α stock, 100 μl of reaction mixture, 50 μl of ligand stock (Final [Ligand] = 0.1 nM). When 40 X stock solutions of test compounds in DMSO were prepared, then the above protocol was used except instead 5 μl test compound or DMSO and 45 μl CXCR2 assay buffer were used. The assay plates were shaken for 5 minutes on a plate shaker, then incubated for 2-8 hours before cpm/well were determined in Microbeta Trilux counter (PerkinElmer). % Inhibition of total binding minus non-specific binding (250 nM Gro-α or 50 μM antagonist) was determined and IC50

values calculated. Compounds of this invention had an IC_{50} of <5μM. The most preferred compounds had a K_i within the range of 0.8nM to 40nM. The compound of Example 360.31 had a K_i of 3nM.

Calcium Fluorescence Assay (FLIPR)

HEK 293 cells stably transfected with hCXCR2 and Gαι/q were plated at 10,000 cells per well in a Poly-D-Lysine Black/Clear plate (Becton Dickinson) and incubated 48 hours at 5% CO_2, 37°C. The cultures were then incubated with 4 mM fluo-4, AM (Molecular Probes) in Dye Loading Buffer (1% FBS, HBSS w. Ca & Mg, 20 mM HEPES (Cellgro), 2.5 mM Probenicid (Sigma) for 1 hour. The cultures were washed with wash buffer (HBSS w Ca, & Mg, 20 mM HEPES, Probenicid (2.5 mM)) three times, then 100 μl/well wash buffer was added.

During incubation, compounds were prepared as 4X stocks in 0.4% DMSO (Sigma) and wash buffer and added to their respective wells in the first addition plate. IL-8 or GRO-α (R&D Systems) concentrations were prepared 4X in wash buffer + 0.1% BSA and added to their respective wells in second addition plate.

Culture plate and both addition plates were then placed in the FLIPR imaging system to determine change in calcium fluorescence upon addition of compound and then ligand. Briefly, 50 μl of compound solutions or DMSO solution was added to respective wells and change in calcium fluorescence measured by the FLIPR for 1 minute. After a 3 minute incubation within the instrument, 50 μl of ligand was then added and the change in calcium fluorescence measured by the FLIPR instrument for I minute. The area under each stimulation curve was determined and values used to determine % Stimulation by compound (agonist) and % Inhibition of Total Calcium response to ligand (0.3 nM IL-8 or GRO-α) for IC50 values of the test compounds.

Chemotaxis assays for 293-CXCR2

A chemotaxis assay is setup using Fluorblok inserts (Falcon) for 293-CXCR2 cells (HEK-293 cells overexpressing human CXCR2). The standard protocol used at present is as follows:

1. Inserts are coated with collagenIV (2ug/ml) for 2 hrs at 37°C.
2. The collagen is removed and inserts are allowed to air dry overnight.

3. Cells are labeled with 10uM calcein AM (Molecular Probes) for 2 hrs. Labeling is done in complete media with 2% FBS.
4. Dilutions of compound are made in minimal media (0.1% BSA) and placed inside the insert which is positioned inside the well of a 24 well plate. Within the well is IL-8 at a concentration of 0.25nM in minimal media. Cells are washed and resuspended in minimal media and placed inside the insert at a concentration of 50,000 cells per insert.
5. Plate is incubated for 2hrs and inserts are removed and placed in a new 24 well. Fluorescence is detected at excitation=485 nM and emission=530 nM.

Cytotoxicity Assays

A cytotoxicity assay for CXCR2 compounds is conducted on 293-CXCR2 cells. Concentrations of compounds are tested for toxicity at high concentrations to determine if they may be used for further evaluation in binding and cell based assays. The protocol is as follows:

1. 293-CXCR2 cells are plated overnight at a concentration of 5000 cells per well in complete media.
2. Dilutions of compound are made in minimal media w/0.1% BSA. Complete media is poured off and the dilutions of compound are added. Plates are incubated for 4, 24 and 48hrs. Cells are labeled with 10uM calcein AM for 15 minutes to determine cell viability. Detection method is the same as above.

Soft Agar Assay

10,000 SKMEL-5 cells/well are placed in a mixture of 1.2% agar and complete media with various dilutions of compound. Final concentration of agar is 0.6%. After 21 days viable cell colonies are stained with a solution of MTT (1mg/ml in PBS). Plates are then scanned to determine colony number and size. IC_{50} is determined by comparing total area vs. compound concentration.

Compounds of formulas IA, IB, 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088 may be produced by processes known to those skilled in the art, by the processes disclosed in WO 02/083624 published October 24, 2002, and by the preparations and examples below.

The invention disclosed herein is exemplified by the following preparations and examples that should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures may be apparent to those skilled in the art.

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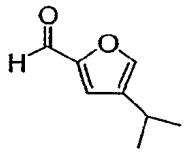
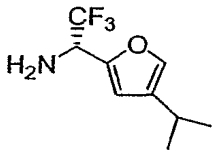
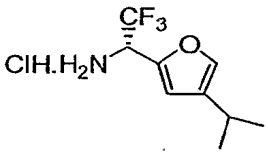
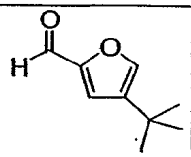
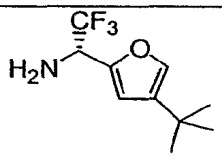
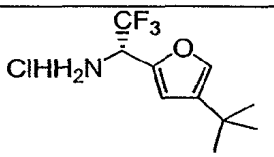
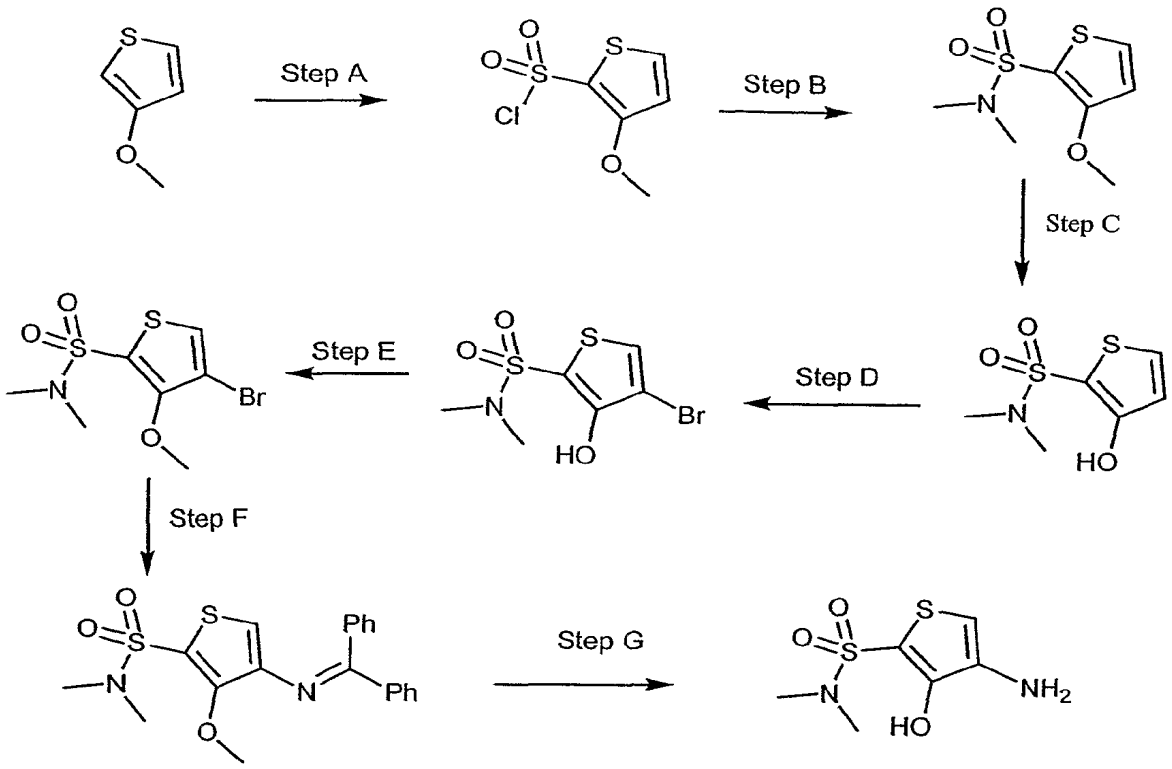
PREPARATIVE EXAMPLES 13.17A-13.17B

Following the procedure set forth in Preparative Example 13.13 of WO 02/083624 published October 24, 2002, but using the prepared or commercially available aldehydes, the optically pure amine products in the Table below were 10 obtained. The number "34.8" in the "Aldehyde" column refers to Preparative Example 34.8 in WO 02/083624.

Prep Ex.	Aldehyde	Amine	Product	Yield (%)
13.17A	34.8 			38%
13.17B				31%

PREPARATIVE EXAMPLE 13.29



Step A

To a solution of 3-methoxythiophene (3 g) in dichloromethane (175 mL) at –78°C was added chlorosulfonic acid (8.5 mL) dropwise. The mixture was stirred for 15 min at –78°C and 1.5 h at room temp. Afterwards, the mixture was poured carefully into crushed ice, and extracted with dichloromethane. The extracts were washed with brine, dried over magnesium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.2 g).

Step B

The product from Step A above (4.5 g) was dissolved in dichloromethane (140 mL) and added with triethylamine (8.8 mL) followed by diethyl amine in THF (2*M*, 21 mL). The resulting mixture was stirred at room temperature overnight. The mixture was washed with brine and saturated bicarbonate (aq) and brine again, dried over sodium sulfate, filtered through a 1-in silica gel pad. The filtrate was concentrated in vacuo to give the desired compound (4.4 g).

Step C

The product from Step B above (4.3 g) was dissolved in dichloromethane (125 mL) and cooled in a -78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 24.3 mL) was added. The mixture was stirred for 4 h while the temperature was increased slowly from -78°C to 10°C. H_2O was added, the two layers were separated, and the aqueous layer was extracted with dichloro- methane. The combined organic layer and extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 3.96 g of the desired hydroxy-compound.

Step D

The product from step C above (3.96 g) was dissolved in 125 mL of dichloromethane, and added with potassium carbonate (6.6 g) followed by bromine (2 mL). The mixture was stirred for 5 h at room temperature, quenched with 100 mL of H_2O. The aqueous mixture was addjusted to pH ~ 5 using a 0.5N hydrogen chloride aqueous solution, and extracted with dichloromethane. The extracts were washed with a 10 % $Na_2S_2O_3$ aqueous solution and brine, dried over sodium sulfate, and filtered through a celite pad. The filtrate was concentrated in vacuo to afford 4.2 g of the desired bromo-compound.

Step E

The product from Step D (4.2 g) was dissolved in 100 mL of acetone and added with potassium carbonate (10 g) followed by iodomethane (9 mL). The mixture was heated to reflux and continued for 3.5 h. After cooled to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo to a dark brown residue, which was purified by flash column chromatography eluting with dichloromethane-hexanes (1:1, v/v) to give 2.7 g of the desired product.

Step F

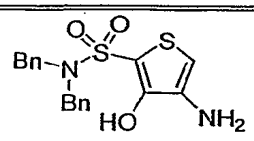
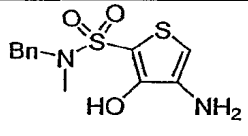
The product from step E (2.7 g) was converted to the desired imine compound (3 g), following the similar procedure to that of Preparative Example 13.19 step D.

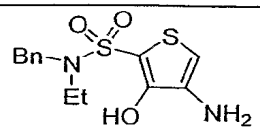
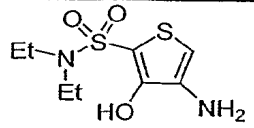
Step G

The imine product from step F (3 g) was dissolved in 80 mL of dichloromethane and cooled in a –78°C bath. A solution of boron tribromide (1.0 M in dichloromethane, 9.2 mL) was added dropwise. The mixture was stirred for 4.25 h from -78°C to 5°C. H_2O (50 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layer and extracts were combined, washed with brine, and concentrated to an oily residue. The residue was dissolved in 80 mL of methanol, stirred with sodium acetate (1.5 g) and hydroxyamine hydrochloride (0.95 g) at room temperature for 2 h. The mixture was poured into an aqueous mixture of sodium hydroxide (1.0 M aq, 50 mL) and ether (100 mL). The two layers were separated. The aqueous layer was washed with ether three times. The combined ether washings were re-extracted with H_2O once. The aqueous layers were combined, washed once with dichloromethane, adjusted to pH ~ 6 using 3.0 M and 0.5 M hydrogen chloride aqueous solutions, and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 1.2 g of desired amine compound.

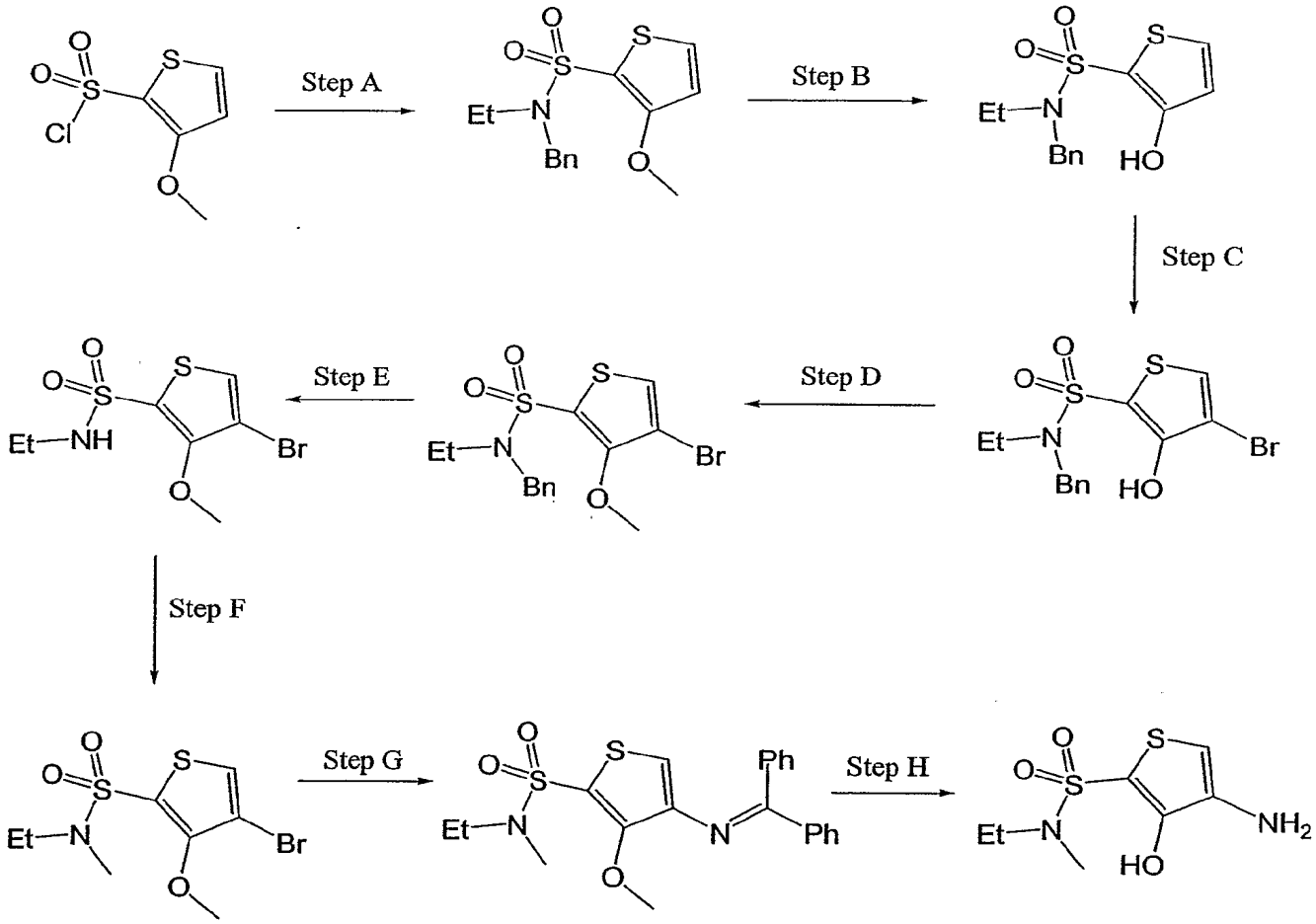
PREPARATIVE EXAMPLES 13.30-13.32

Following the procedures set forth in Preparative Example 13.29, but using commercially available amines, hydroxy-amino-thiophene products in the Table below were obtained.

Prep Ex.	Amine	Product	Yield (%) MH^+
13.30	Bn_2NH		10% 375.1
13.31	MeBnNH		14% 299.0

13.32	EtBnNH		22%
13.32A	$(Et)_2NH$		25%

PREPARATIVE EXAMPLE 13.33



Step A

2-Chlorosulfonyl-3-methoxy-thiophene (4.0 g, 18.8 mmol), the product from Step A of Preparative Example 13.29, was converted to 3-methoxy-2-ethylbenzylsulfonyl-thiophene (5.5 g, 94%, MH^+ = 312.1) by using ethylbenzylamine, following the procedure set forth in Preparative Example 13.29, Step B.

Step B

The product from Step A above (5.5 g, 17.70 mmol) was demethylated following the procedure set forth in Preparative Example 13.29, Step C. The alcohol product was obtained in 4.55 g (87%, MH^+ = 298.0).

Step C

The product from Step B above (4.55 g, 15.30 mmol) was brominated using the procedure set forth in Preparative Example 13.29, Step D. The corresponding bromide was obtained in 4.85 g (84%).

Step D

The bromo-alcohol from Step C above (4.84 g, 12.86 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E. The product was obtained in 4.82 g (96%).

Step E

The product from Step D above (4.82 g, 12.36 mmol) was stirred with concentrated sulfuric acid (5 mL) at room temperature for 3 h. Ice water (30 mL) was added to the mixture followed by CH_2Cl_2 (50 mL). The aqueous mixture was adjusted to pH ~ 6 using a 1.0 M NaOH aqueous solution. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to a dark brown oil, which was purified by flash column chromatography, eluting with CH_2Cl_2-hexanes (1:1, v/v). Removal of solvents afforded 3.03 g (82%) of the debenzylated product (M^+ = 300.0, M+2 = 302.0).

Step F

The product from Step E (1.34 g, 4.45 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E. The desired product was obtained in 1.36 g (97%, M^+ = 314.1, M+2 = 316.0).

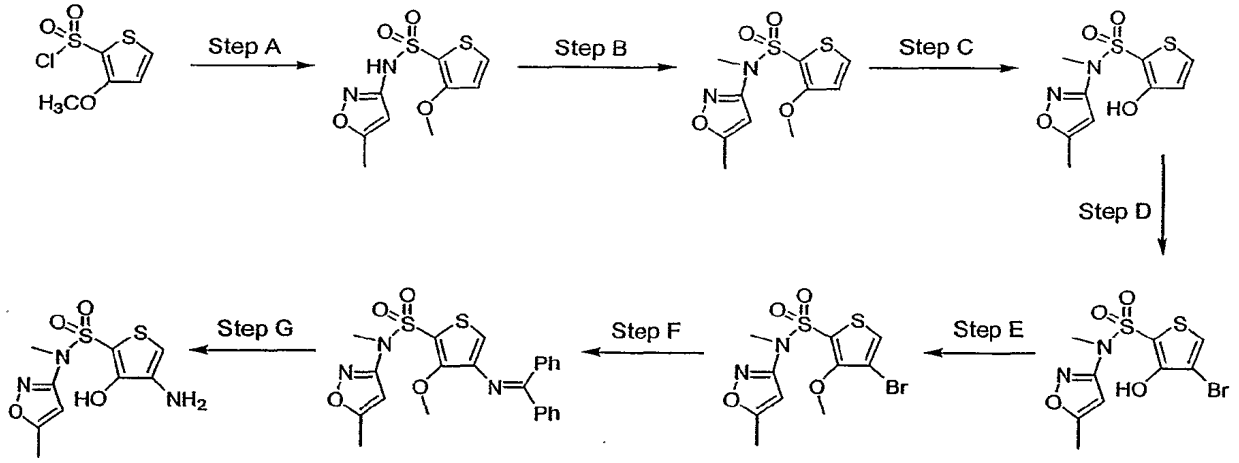
Step G

The product from Step F (1.36 g, 4.33 mmol) was converted to imine product (1.06 g, 55%, MH^+ = 415.1) using the procedure set forth in Preparative Example 13.29, Step F.

Step H

The imine product from Step G (1.06 g, 2.56 mmol) was converted to the desired hydroxy-amino thiophene compound (0.26 g, 43%) using the procedure set forth in Preparative Example 13.29, Step G.

PREPARATIVE EXAMPLE 13.34



Step A

2-Chlorosulfonyl-3-methoxy-thiophene (3.8 g, 17.87 mmol), the product from step A of Preparative Example 13. 29, was dissolved in 100 mL of CH_2Cl_2 and 20 mL of pyridine. 3-Amino-5-methyl-isoxazole (3.5 g, 35.68 mmol) was added. The mixture was stirred for 20 h at room temperature, diluted with 100 mL of CH_2Cl_2, and washed with a 0.5 N HCl aqueous solution (50 mL x 2), H_2O (50 mL), and brine (50 mL). The organic solution was dried with Na_2SO_4, and concentrated in vacuo to a brown oil.

This oil was dissolved in 100 mL of CH_2Cl_2, washed again with a 0.5 M HCl aqueous solution (30 mL x 3) and brine. After dried over Na_2SO_4, the organic solution was concentrated in vacuo to a yellow solid, 4.48 g (91%, MH^+= 275.0) of the desired product.

Step B

The product from Step A above (4.48 g, 16.33 mmol) was dissolved in acetone (100 mL), added with potassium carbonate (5.63 g, 40.80 mmol) and iodomethane (10.1 mL, 163.84 mmol). The mixture was stirred at room temperature for 1.5 h, diluted with 100 mL of hexanes and 50 mL of CH2Cl2, and filtered through a 1-in silica gel pad, rinsing with CH_2Cl_2. The filtrate was concentrated under reduced pressure to give 4.23 g (90%, MH^+= 289.0) of the desired product as a light yellow solid.

Step C

To a stirred suspension of sodium hydride (130 mg, 95%, 5.4 mmol) in 8 mL of *N*, *N'*-dimethylforamide at room temperature was added ethanethiol (0.45 mL, 6.0 mmol) dropwise. After 5 min, the mixture became a clear solution, and was added to a stirred solution of the product obtained from Step B above (0.45 g, 1.56 mmol) in 2 mL of *N*, *N'*-dimethylforamide in a round bottom flask. The flask was sealed with a ground glass stopper, and the mixture was heated at 90-95°C for 4 h. After cooled to room temperature, the mixture was poured into 20 mL of a 1.0 M NaOH aqueous solution, further rinsed with 20 mL of H_2O. The aqueous mixture was washed with diethyl ether (30 mL x 2), adjusted to PH ~5 using a 0.5 M HCl aqueous solution, and extracted with CH_2Cl_2 (50 mL x4). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to a dark yellow solution. This was dissolved in 50 mL of ethyl acetate, washed with H_2O (30 mL x2) and brine (30 mL), dried over Na_2SO_4. Evaporation of solvent gave 0.422 g of the alcohol product (99%, MH^+ = 275.0).

Step D

The alcohol obtained from Step C above (0.467 g, 1.70 mmol) was brominated using the procedure set forth in Preparative Example 13.29, Step D, to afford the corresponding bromide in 0.607 g (100%).

Step E

The bromide obtained from Step D above (0.607 g, 1.72 mmol) was methylated using the procedure set forth in Preparative Example 13.29, Step E, to give the desired product in 0.408 g (65%, M^+ = 367, M+2 = 369.1).

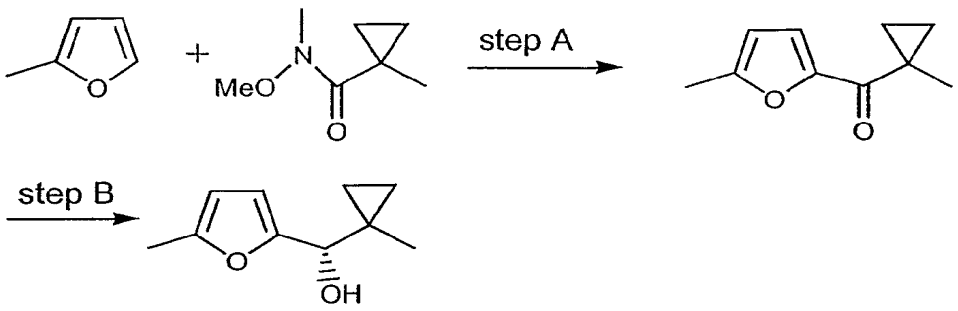
Step F

The product (0.405 g, 1.103 mmol) from Step E above was converted to the imine compound (0.29 g, 56%) using the procedure set forth in Preparative Example 13.29, Step F.

Step G

The imine product obtained from Step F above (0.29 g, 0.61 mmol) was demethylated using the procedure set forth in Step C above to give the corresponding alcohol as a dark yellow oil, which was dissolved in 5 mL methanol and added with sodium acetate (0.12 g, 1.46 mmol) and hydroxyamine hydrochloride (0.075 g, 1.08 mmol). The resulting mixture was stirred at room temperature for 3 h, and poured into 10 mL of 1.0 M NaOH aqueous solution. 30 mL of H_2O was used as rinsing and combined to the aqueous layer. The aqueous mixture was washed with diethyl ether (40 mL x 3), adjusted to pH ~ 6 using a 1.0 M HCl aqueous solution, and extracted with ethyl acetate (40 mL x 3). The organic extracts were washed with H_2O (20 mL x2), brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo to give 0.112 g of the desired hydroxy-amino thiophene sulfonamide (64%, MH^+ = 290).

PREPARATIVE EXAMPLE 13.35



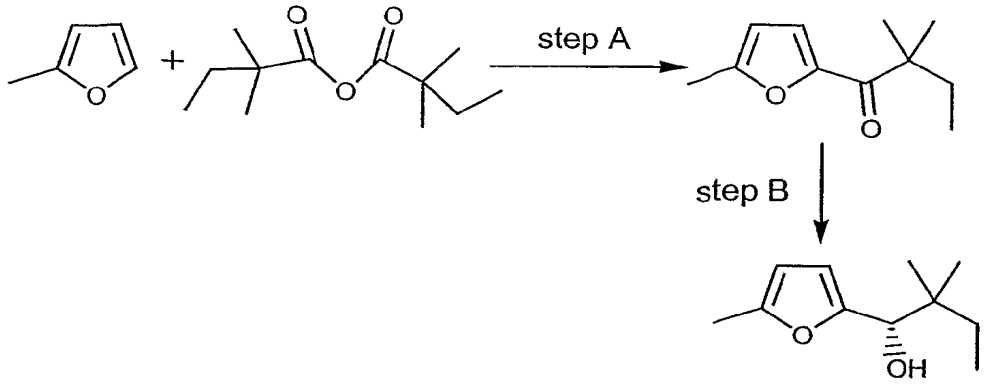
Step A

To a solution of 2-methyl furan (1.72g) in ether was added BuLi (8.38mL) at –78^{0}C and stirred at room temperature for half an hour. The reaction mixture again cooled to –78^{0}C and quenched with cyclopropyl amide **1** and stirred for two hours at –78^{0}C and slowly warmed to room temperature. The reaction mixture stirred for three hours at room temperature and quenched with the addition of saturated ammonium chloride solution. The mixture was taken to a separatory funnel, washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using column chromatography to afford the ketone 3.0g (87%) as a pale yellow oil.

Step B

To a solution of ketone (1.0g) in THF (5.0mL) at 0^{0}C was added R-methyl oxazoborolidine (1.2Ml, 1M in toluene) dropwise followed by addition of a solution of borane complexed with dimethyl sulfide (1.85mL, 2M in THF). The reaction mixture was stirred for 30minutes at 0^{0}C and than at room temperature for one hour. The reaction mixture was cooled to 0^{0}C and MeOH was added carefully. The mixture was stirred for 20 minutes and was concentrated under reduced pressure. The residue was extracted with ether, washed with water, 1M HCl (10mL), saturated sodium bicarbonate (10.0mL) water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and removal of solvent afforded the crude alcohol which was purified by silica gel chromatography to afford the pure alcohol 0.91g (91%) as yellow oil.

PREPARATIVE EXAMPLE 13.36



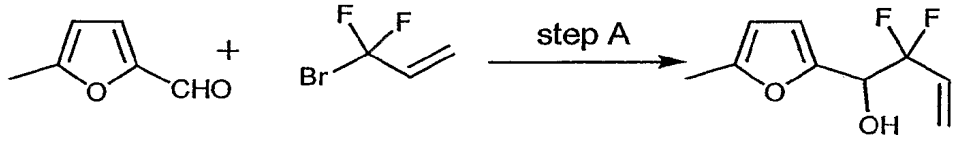
Step A

An equimolar mixture of 2-methylfuran (1.0g) and anhydride (2.6g) was mixed with $SnCl_4$ (0.05mL) and heated at 100^0C for 3 hours. After cooling the reaction mixture, water (10mL) was added, followed by saturated sodium carbonate solution until it becomes alkaline. The reaction mixture was extracted with ether several times and the combined ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was purified by using silica gel chromatography to afford the ketone 0.9g (43%) as a yellow oil.

Step B

The Step B alcohol was obtained following a similar procedure set forth in the Preparative Eexample 13.35 Step B.

PREPARATIVE EXAMPLE 13.37

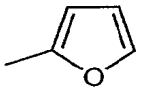
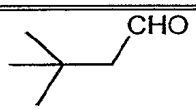
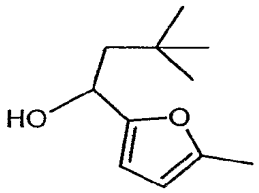
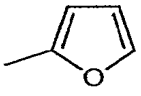
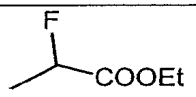
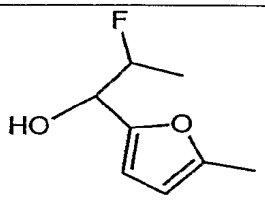
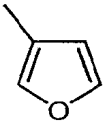
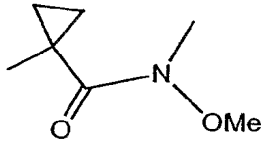
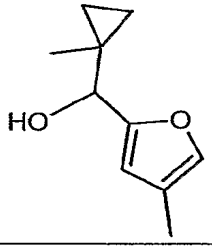
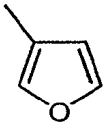
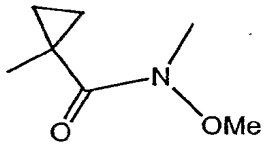
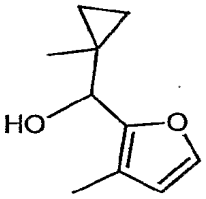
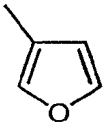
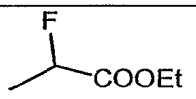
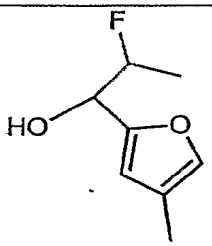
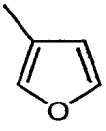
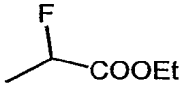
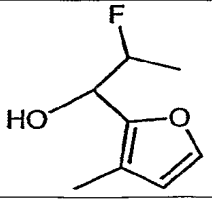


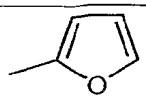
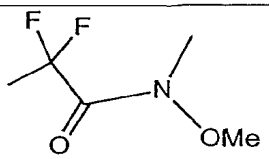
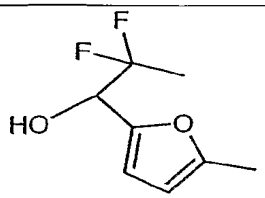
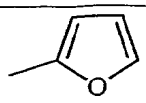
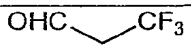
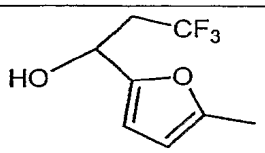
Step A:

To a solution of 5-methyl furan-2-aldehyde (1.0g) and 3-bromo-3,3-difluoropropene (2.24g) in DMF (30mL) was added indium powder (1.66g) and lithium iodide (50.0mg). The reaction mixture was stirred over night, diluted with water and extracted with ether. The ether layer was washed with water, brine and purified by silicagel chromatography to afford the pure alcohol 2.8g (92%).

PREPARATIVE EXAMPLES 13.38-13.45

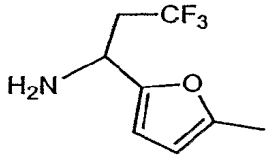
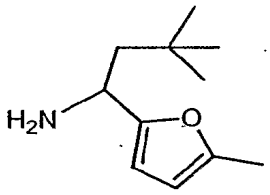
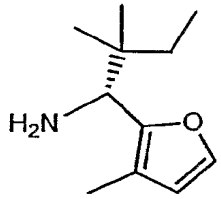
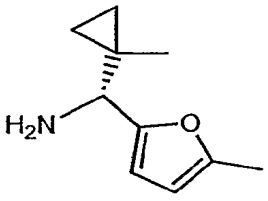
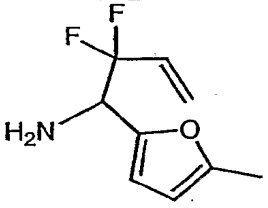
Following a similar procedure set forth in Preparative Example 13.25 of WO 02/083624 published October 24, 2002, and Preparative Example 13.35, and using the indicated Furan and Electrophile, the following Alcohols in the Table below were prepared.

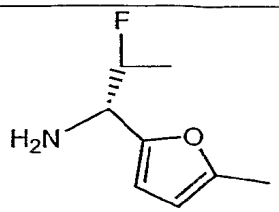
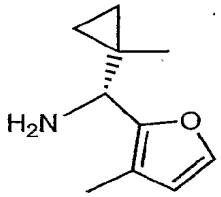
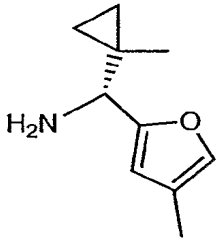
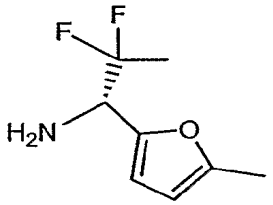
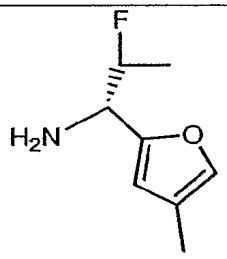
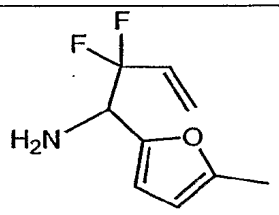
Prep. Ex	Furan	Electrophile	Alcohol	Yield
13.38				86%
13.39				69%
13.40				84%
13.41				82%
13.42				60%
13.43				65%

13.44				82%
13.45				89%

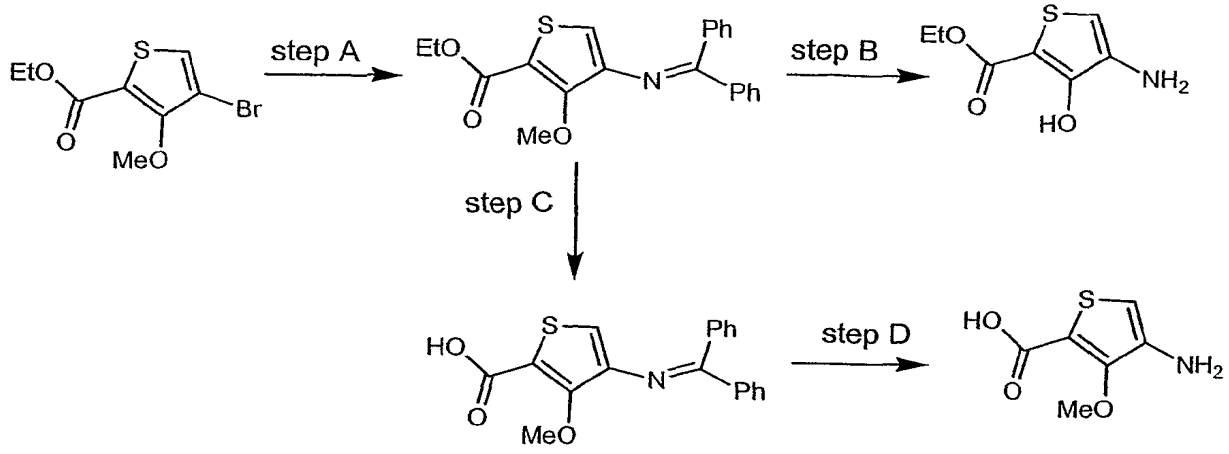
PREPARATIVE EXAMPLES 13.50-13.61

Following a similar procedure set forth in Preparative Examples 13.25 of WO 02/083624 published October 24, 2002, and using the indicated Alcohol, the following Amines in the Table below were prepared.

PREP. EX.	ALCOHOL	AMINE	% YIELD
13.50	13.45		28%
13.51	13.38		58%
13.52	13.36		69%
13.53	13.35		81%
13.54	13.37		82%

13.55	13.39		45%
13.56	13.41		57%
13.57	13.40		58%
13.58	13.44		54%
13.59	13.42		53%
13.61	13.37		82%

PREPARATIVE EXAMPLE 13.70



Step A

The imine was prepared following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, from the known bromoester (1.0g) as a yellow solid, Step A to yield 1.1g (79%).

Step B

The Step A product (0.6g) was reacted following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, to give the amine product 0.19g (64%).

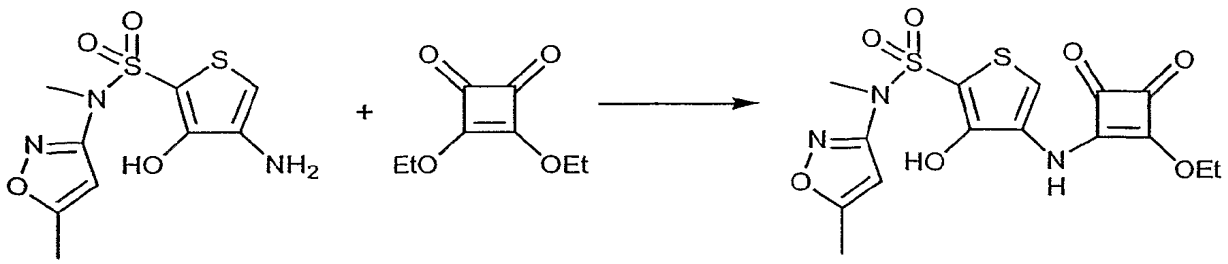
Step C

The Step B product (1.0g) was reacted following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, to give the acid as yellow solid 0.9g (94%)

Step D

The Step C product (0.35g) was reacted following the procedure set forth in the Preparative Example 13.19 of WO 02/083624 published October 24, 2002, to give the amino acid as yellow solid 0.167g (93%).

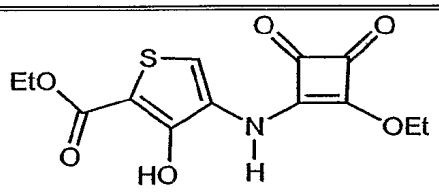
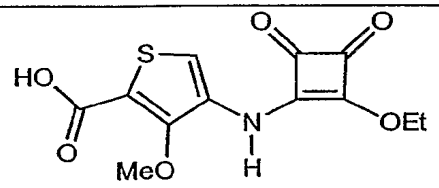
PREPARATIVE EXAMPLE 19.2



The hydroxy thiophene amine from Preparative Example 13.34 (108 mg, 0.37mmol) was dissolved in 5 mL of ethanol and stirred with diethoxysquarate (0.14 mL, 0.95 mmoL) and potassium carbonate (52 mg, 0.38 mmol) at room temperature overnight. The mixture was diluted with H2O (25 mL), adjusted to pH ~ 6 using a 1.0 M HCl aqueous solution, and extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with brine, dried over Na2SO4, and concentrated to an oil, which was purified by flash column chromatography, eluting with CH2Cl2-MeOH (100:1, v/v). Removal of solvents afforded 83.5 mg of the titled product (MH+ = 414).

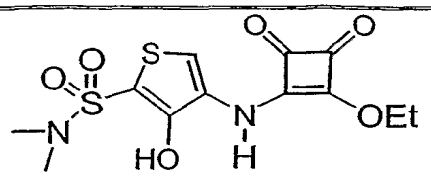
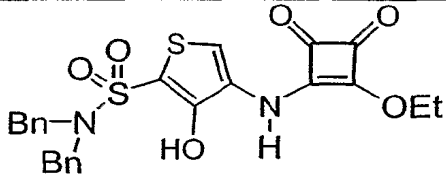
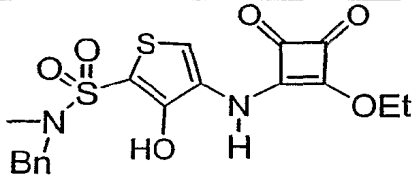
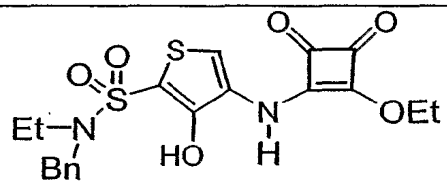
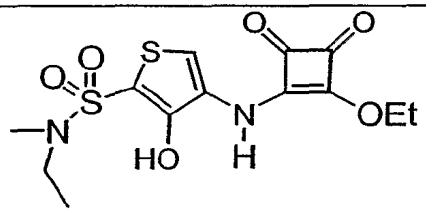
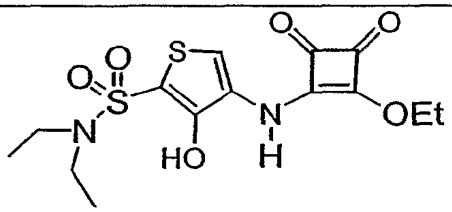
PREPARATIVE EXAMPLES 23.14A and 23.14B

Following the procedures set forth in Preparative Example 19 of WO 02/083624 published October 24, 2002, but using the amine from the Preparative Example indicated in the Table below, the cyclobutenedione intermediates were obtained.

Prep Ex.	Amine from Prep Ex.	Product	1. Yield (%) 2. MH^+
23.14A	13.70 Step B		1. 60% 2. 138
23.14B	13.70 Step D		1. 65%

PREPARATIVE EXAMPLE 23.15A –23.15F

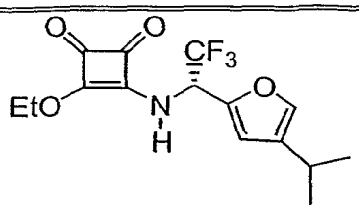
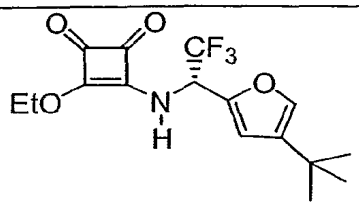
Following the procedures set forth in Preparative Example 19.2 but using the amines from the Preparative Example indicated in the Table below, the corresponding cyclobutenedione intermediates were prepared.

Prep Ex.	Amine from Prep Ex.	Product	1. Yield (%) 2. MH^+
23.15A	13.29		1. 66 % 2. 347
23.15B	13.30		1. 21% 2. 499
23.15C	13.31		1. 41% 2. 423
23.15D	13.32		1. 26% 2. 437
23.15E	13.33		1. 48% 2. 361.1
23.15F	13.32A		1. 68% 2. 375.1

PREPARATIVE EXAMPLE 23.16-23.26

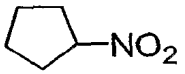
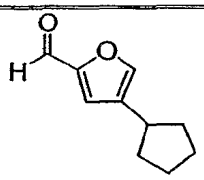
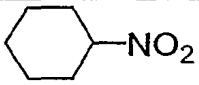
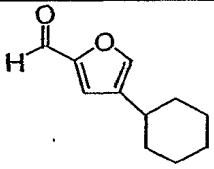
Following the procedures set forth in Preparative Example 19 of WO 02/083624 published October 24, 2002, but using the amine from the Preparative Example

indicated in the Table below, the cyclobutenedione intermediate products were obtained.

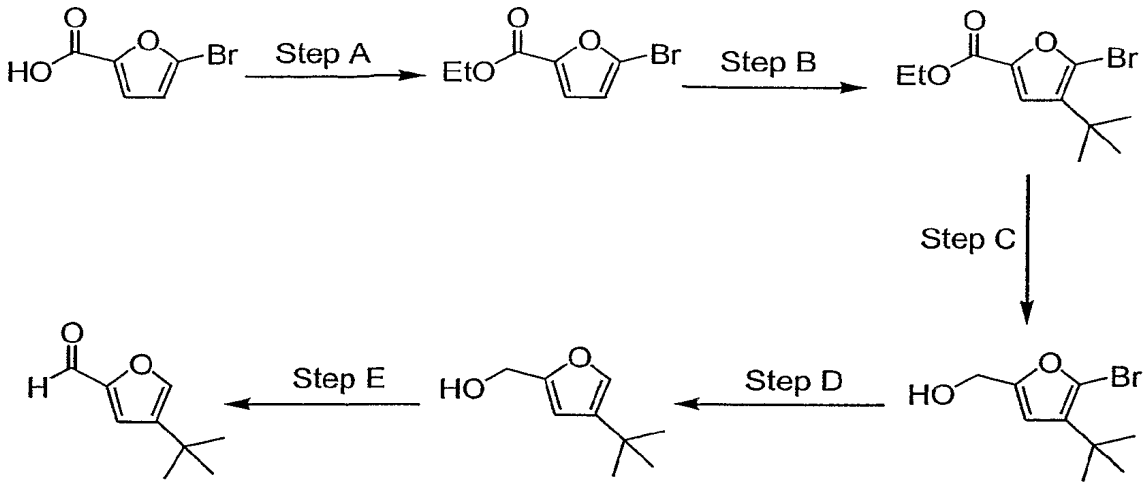
Prep Ex.	Amine from Prep Ex.	Product	Yield (%)
23.25	13.17A		48%
23.26	13.17B		66%

PREPARATIVE EXAMPLE 34.15-34.16

Following the procedures set forth in Preparative Example 34.8 of WO 02/083624 published October 24, 2002, but using the nitroalkanes indicated in the table below, the aldehydes were prepared.

Prep. Ex.	Nitroalkane	Aldehyde	Yield
34.15			17%
34.16			21%

PREPARATIVE EXAMPLE 34.17



Step A

To a stirred suspension of 5-bromo-2-furoic acid (15.0 g, 78.54 mmol) in 225 mL of CH_2Cl_2 at room temperature was added oxalyl chloride followed by a catalytic amount of *N,N'*-dimethylforamide. After 1 h, ethanol (20 mL) was added followed by triethylamine (22 mL). Reaction was continued for 15 h. The mixture was concentrated under reduced pressure to a residue, which was extracted with excess volume of hexanes, and hexanes-CH_2Cl_2 (3:1, v/v). The extracts were filtered, the filtrated was concentrated to a yellow oil, dried on high vacuum, yielding 17.2 g (93%) of the desired ester.

Step B

The ester product obtained from Step A above (17.2 g, 73.18 mmol) was converted to 2-ethyl-4-tertbutyl-5-bromo-furoate (7.9 g, 37%) using the literature procedure: *J. Am. Chem.Soc.*, **1939**, *61*, 473-478.

Step C

The ester product obtained from Step B above (7.9 g, 27.13 mol) was reduced to the alcohol (6.32 g) using the procedure set forth in Preparative Example 34.8, Step C, of WO 02/083624 published October 24, 2002.

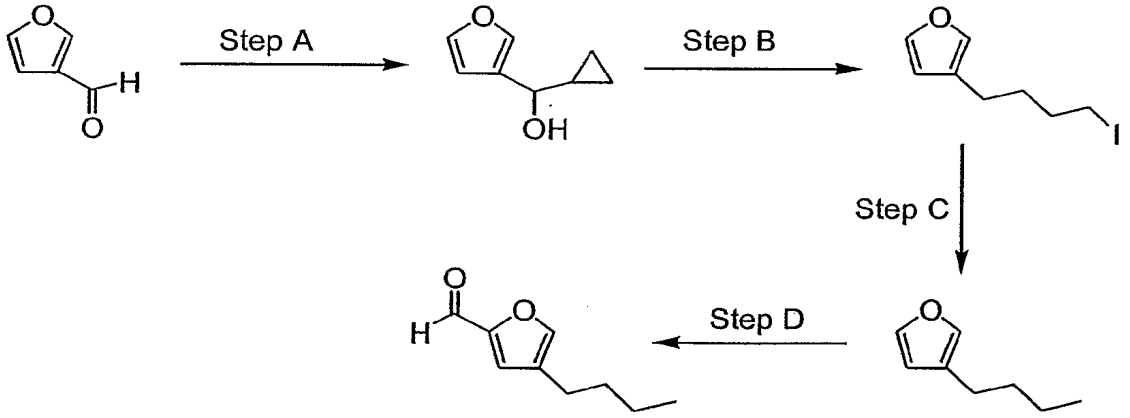
Step D

The product obtained from Step C above (6.32 g) was dissolved in 140 mL of THF and cooled in a –78°C bath. A 2.5 M solution of n-butyllithium in hexanes (22 mL, 55.0 mmol) was added dropwise along the side wall of the flask. After 15 min, H_2O (~70 mL) was added. Cooling bath was removed, the mixture was stirred for an additional 1h. Brine (50 mL) and CH_2Cl_2 (300 mL) were added, the two layers were separated, the aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers ere dried by Na_2SO_4. Evaporation of solvents afforded 5.33 g (crude) of the debrominated product as a reddish brown oil.

Step E

The alcohol product obtained from Step D above (5.33g) was oxidized to the corresponding aldehyde (3.06 g, 74% over three steps) using the procedure set forth in Preparative Example 34.8, Step D.

PREPARATIVE EXAMPLE 34.18



Step A

To a stirred solution of cyclopropyl bromide (4.0 mL, 50 mmol) in 120 mL of ether at –78°C was added dropwise a 1.7M solution of t-butyllithium in pentane (44.5 mL, 75.7 mmol). After 10 min, cooling bath was removed, stirring was continued for 1.5 h. The mixture was cooled again in a –78°C bath, and 3-furaldehyde (3.5 mL, 41.9 mmol) was added. Reaction was continued for 1 h, and quenched with a saturated NH4Cl aqueous solution. The aqueous mixture was extracted with CH_2Cl_2

(100 mL x 3). The organic extracts were washed with brine, dried by Na_2SO_4, filtered, and concentrated in vacuo to give 5.3 g (91%) of the alcohol product as a yellow oil.

Step B

Chloro trimethylsilane (27.2 mL, 214.2 mmol) was added dropwise to a vigorously stirred suspension of sodium iodide (32 g, 213.5 mmol) in 100 mL of acetonitrile. After 5 min, a solution of the alcohol obtained from Step A above (4.93 g, 35.68 mmol) in 100 mL of acetonitrile was added dropwise. Stirring was continued for 5 min. H_2O (100 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (100 mL x 2). The organic layers were combined, washed with a 10 % $Na_2S_2O_3$ aqueous solution and brine, and dried over Na_2SO_4. Evaporation of solvents gave a dark brown oil, which was filtered through a 5-in silica gel column, eluting with CH_2Cl_2-hexanes (1:3.5, v/v). Removal of solvents afforded 4.22 g (47%) of the iodo product as a light yellow oil.

Step C

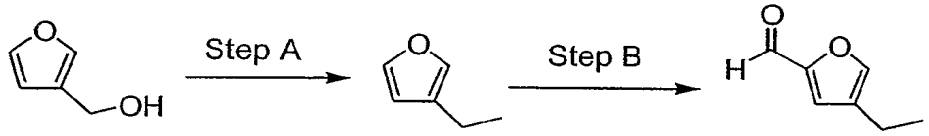
The iodo-product obtained from Step B above (2.2 g, 8.8 mmol) was dissolved in 60 mL of ether, and stirred in a –78°C bath. A 1.7 M solution of t-butyllithium in pentane (10.4 mL, 17.7 mmol) was added dropwise. After 20 min, cooling bath was removed. Reaction was continued for 2.5 h, and quenched with H_2O (20 mL). The aqueous mixture was stirred overnight and separated. The aqueous layer was extracted with ether (30 mL). The combined organic layers were washed with brine, dried by Na_2SO_4, and filtered through a Celite pad. Removal of solvent gave 1.10 g (100%) of 3-butylfuran as a reddish-yellow oil.

Step D

3-Butylfuran (1.1 g, 8.8 mmol), obtained from Step C above, was dissolved in 60 mL of ether, and stirred in a –78°C bath. A 1.7 M solution of t-butyllithium in pentane (6.0 mL, 10.2 mmol) was added dropwise along the side wall of the flask. The mixture was stirred for 3 h from –78°C to 0°C, and continued for 1 h at room temperature. A solution of *N,N'*-dimethylforamide (1.1 mL, 14.23 mmol) was added. Reaction was continued overnight, and quenched with a saturated NH_4Cl aqueous solution. The two layers were separated, the aqueous layer was extracted with

CH_2Cl_2 (30 mL x 2). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated to an oil, which was purified by preparative TLC (CH_2Cl_2-hexanes = 1:1.5, v/v) to give 0.48 g (36%) of the aldehyde (contaminated by some 3-butyl-2-furaldehyde).

PREPARATIVE EXAMPLE 34.19



Step A

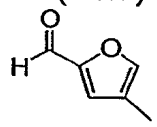
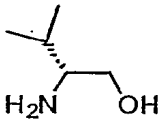
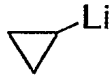
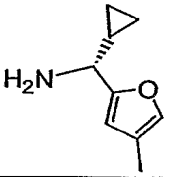
3-Ethylfuran was prepared from 3-hydroxymethylfuran according to literature procedure: *J. Org. Chem.*, **1983**, *48*, 1106-1107.

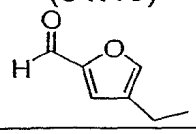
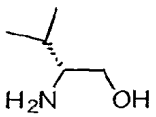
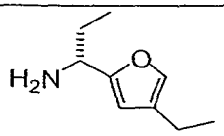
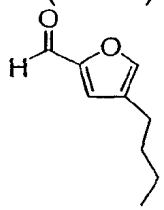
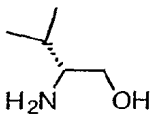
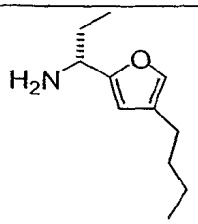
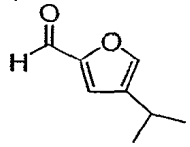
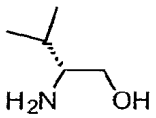
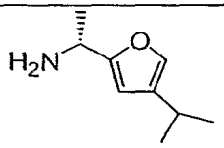
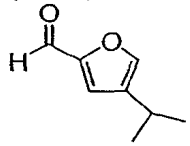
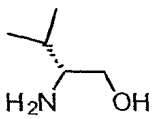
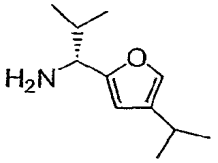
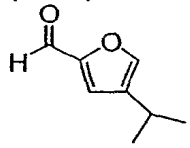
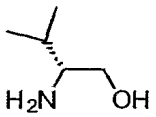
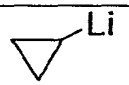
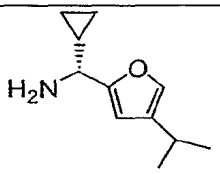
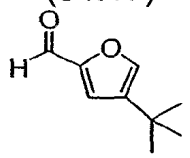
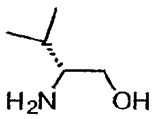
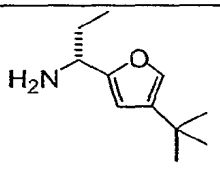
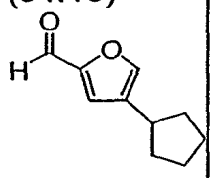
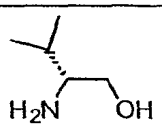
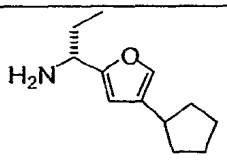
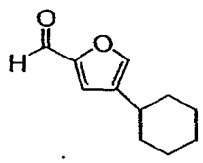
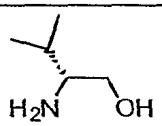
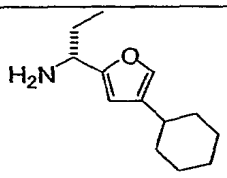
Step B

3-Ethylfuran obtained from Step A above was converted to 4-ethyl-2-furaldehyde using the procedure set forth in Preparative Example 34.32, Step D, of WO 02/083624 published October 24, 2002.

PREPARATIVE EXAMPLES 75.10A-75.10J

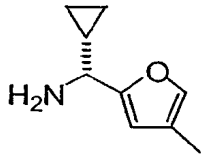
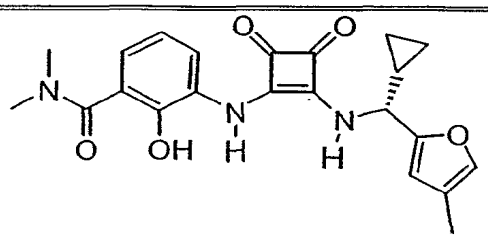
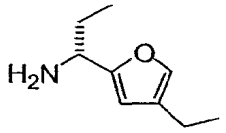
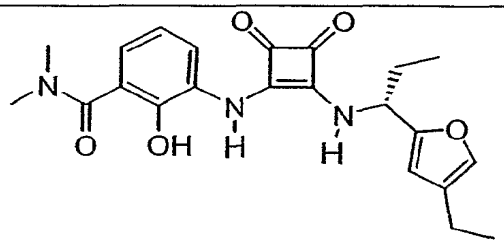
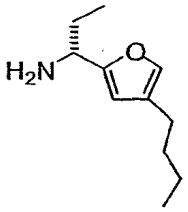
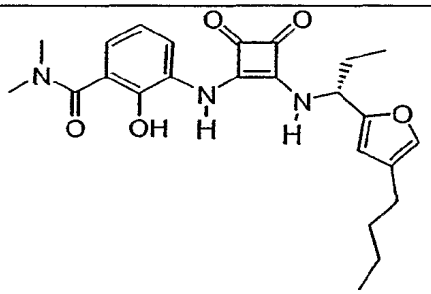
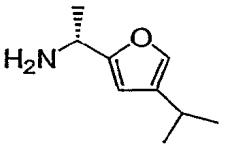
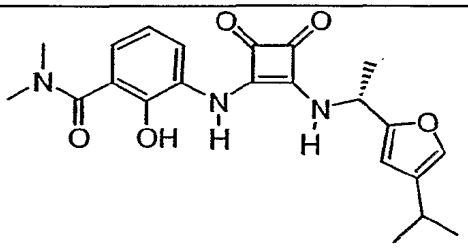
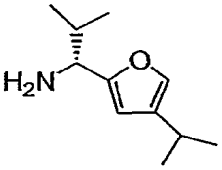
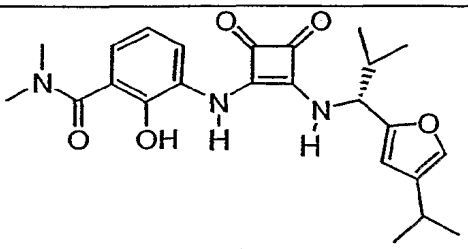
Following the procedure set forth in Preparative Example 64 of WO 02/083624 published October 24, 2002, but using the commercially available aldehydes, amino alcohols, and organolithium reagents in the Table below, the optically pure amine products in the Table below were obtained. The numbers in the "Aldehyde" column refer to preparative examples herein or in WO 02/083624.

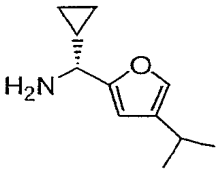
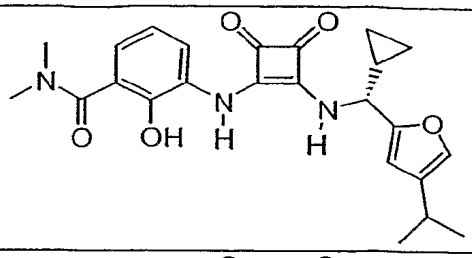
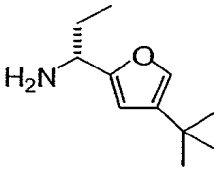
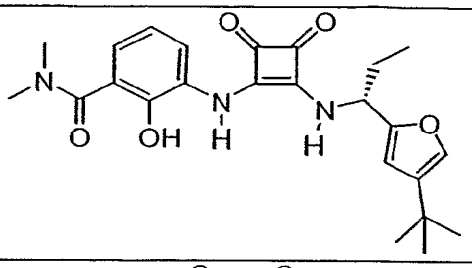
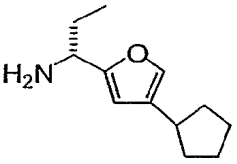
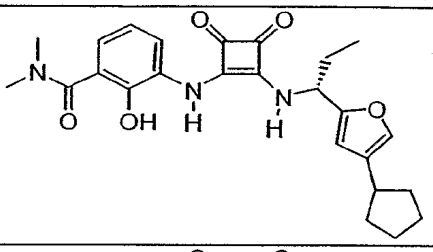
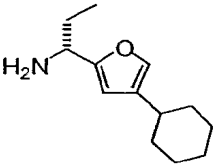
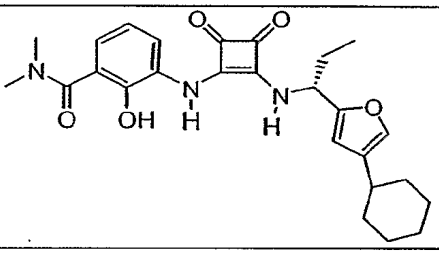
Prep Ex.	Aldehyde	Amino Alcohol	Organo lithium	Product	1.Yield 2. MH^+
75.10A	(34.7) 				1. 61% 2. 135 $[M-NH_2]^+$

75.10B	(34.19) 		EtLi		1. 24% 2. 154
75.10C	(34.18) 		EtLi		1. 32% 2. 165 $[M-NH_2]^+$
75.10D	(34.8) 		MeLi		1. 47% 2. 137 $[M-NH_2]^+$
75.10E	(34.8) 		iPrLi		1. 30% 2. 165 $[M-NH_2]^+$
75.10F	(34.8) 				1. 67% 2. 163.0 $[M-NH_2]^+$
75.10G	(34.17) 		EtLi		1. 24% 2. 165 $[M-NH_2]^+$
75.10H	(34.15) 		EtLi		1. 70% 2. 194
75.10J	(34.16) 		EtLi		1. 54% 2. 208

EXAMPLES 360.109-360.117

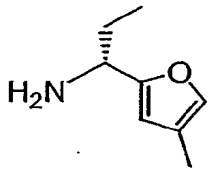
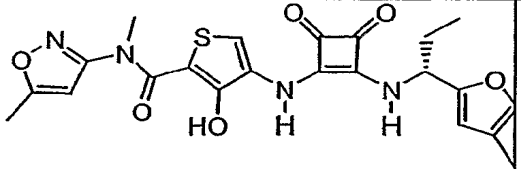
Following the procedure set forth in Example 261 of WO 02/083624 published October 24, 2002, but using the commercially available amine or the prepared amine from the Preparative Example indicated in the table below, the following cyclobutenedione products were obtained.

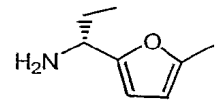
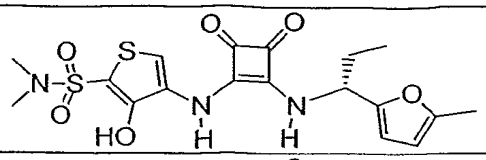
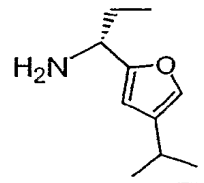
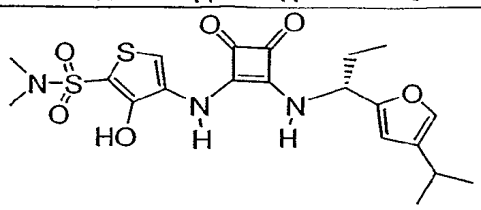
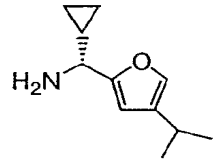
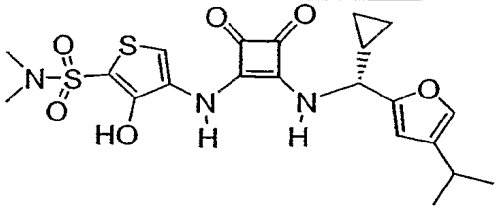
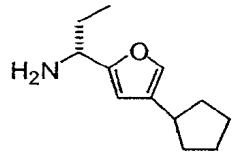
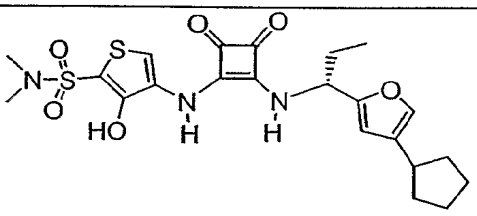
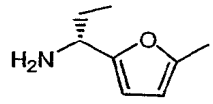
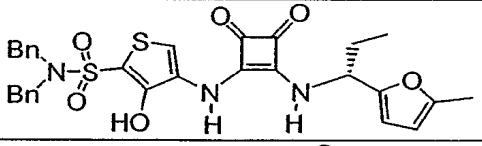
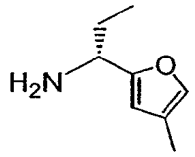
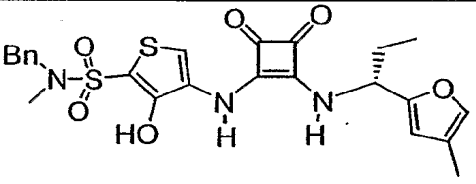
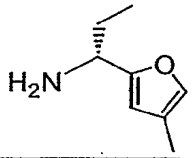
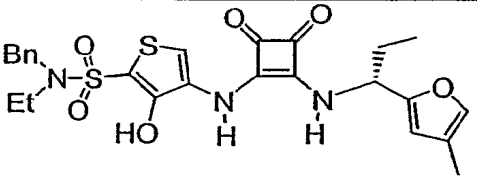
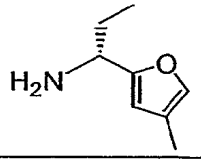
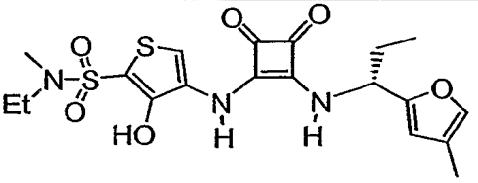
Ex.	Amine	Product	1.Yield 2. MH^+ 3. mp (°C)
360.109	75.10A 		1. 67% 2. 410.1 3. 119-121
360.110	75.10B 		1. 71% 2. 412 3. 102
360.111	75.10C 		1. 64% 2. 440.1 3. 91-93
360.112	75.10D 		1. 79% 2. 412 3. 111-113
360.113	75.10E 		1. 20% 2. 440.1 3. 130 (DEC)

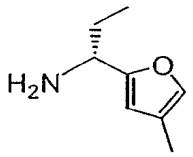
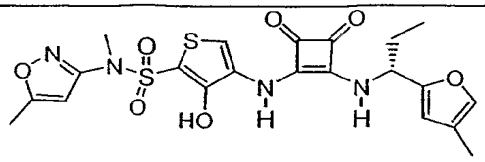
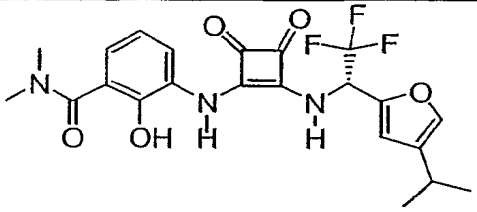
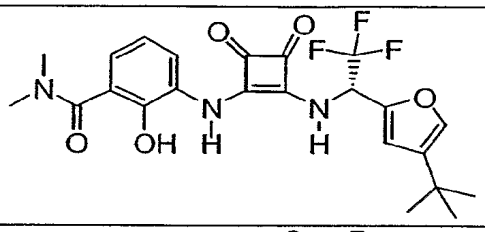
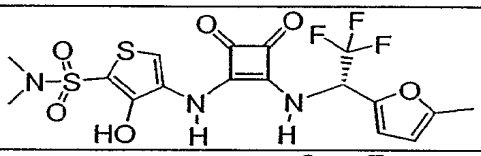
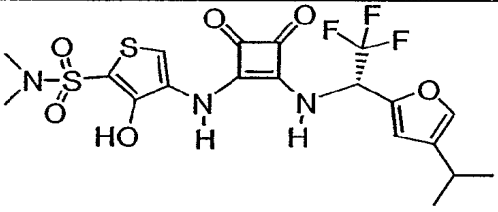
360.114	75.10F 		1. 61% 2. 438.1 3. 117-119
360.115	75.10G 		1. 61% 2. 440.1 3. 117-119
360.116	75.10H 		1. 81% 2. 452 3. 118
360.117	75.10J 		1. 65% 2. 466 3. 109

EXAMPLES 368.32-368.45

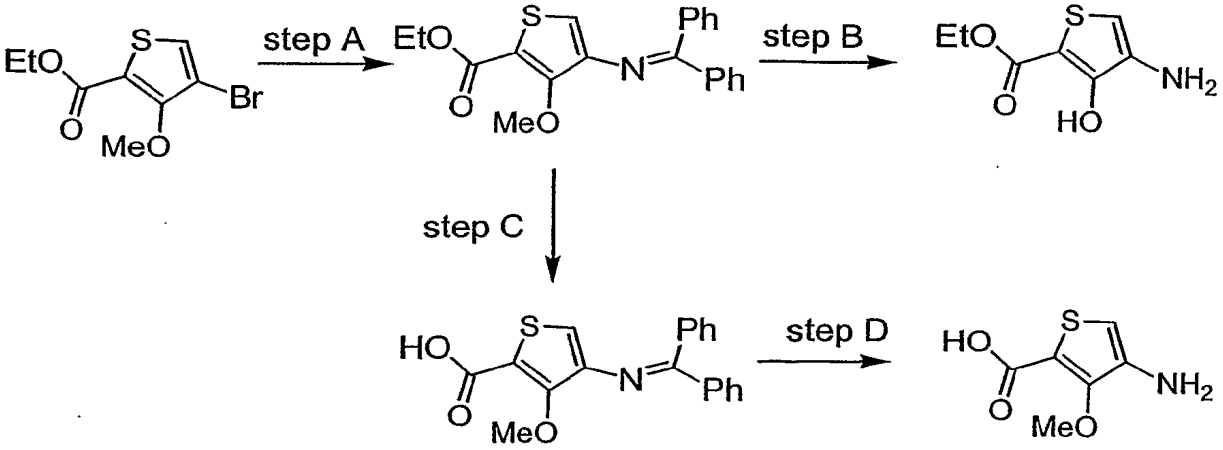
Following the procedure set forth in Example 261 of WO 02/083624 published October 24, 2002, but using the commercially available amine in the table below and the cyclobutenedione intermediate from the Preparative Example indicated, the following cyclobutenedione products were obtained. The numbers in the "Amine" and "Prep. Ex." columns refer to preparative examples herein or in WO 02/083624.

Ex.	Amine	Prep. Ex.	Product	1.Yield (%) 2. MH^+ 3. mp (°C)
368.32	75.49 	23.14		1. 58% 2. 471.1 3. 149

368.33	75.1 	23.15A		1. 33% 2. 440.1 3. 181
368.34	75.9 	23.15A		1. 56% 2. 468 3. 180
368.35	75.10F 	23.15A		1. 28% 2. 480 3. 186
368.36	75.10H 	23.15A		1. 48% 2. 494 3. 112.5
368.37	75.1 	23.15B		1. 58% 2. 592 3. 177-179
368.38	75.49 	23.15C		1. 69% 2. 516 3. 88-90
368.39	75.49 	23.15D		1. 80% 2. 530 3. 134-137
368.40	75.49 	23.15E		1. 57% 2. 454 3. 138-140

368.41	75.49 	19.2		1. 26% 2. 507 3. 162-164
368.42	3	23.25		1. 82% 2. 466 3. 141-143
368.43	3	23.26		1. 67% 2. 480 3. 139 dec
368.44	13.29	23.16		1. 29% 2. 480 3. 112-114
368.45	13.29	23.26		1. 88% 2. 508 3. 190 dec

PREPARATIVE EXAMPLES 600



Step A

Following the procedure set forth in Preparative Example 13.19, Step D, of WO 02/083624, published October 24, 2002, the imine was prepared from the known bromoester (1.0g) to yield 1.1g (79%) as a yellow solid.

Step B

The product of step A (0.6g) was reacted following the procedure set forth in Preparative Example 13.19, Step E, of WO 02/083624, published October 24, 2002, to give the amine product 0.19g (64%).

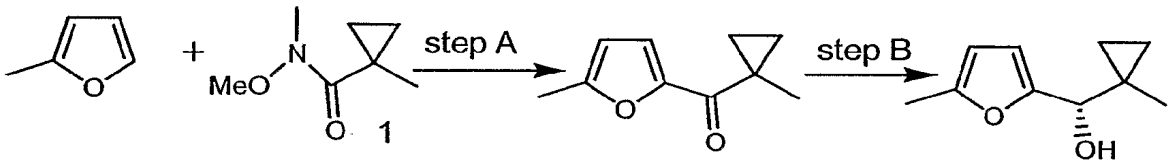
Step C

The product of Step B (1.0g) was reacted following the procedure set forth in Preparative Example 13.19, Step B, of WO 02/083624, published October 24, 2002, to give the acid as yellow solid 0.9g (94%).

Step D

The product of Step C (0.35g) was reacted following the procedure set forth in Preparative Example 13.19, Step E, of WO 02/083624, published October 24, 2002, to give the amino acid as yellow solid 0.167g (93%).

PREPARATIVE EXAMPLES 601



Step A

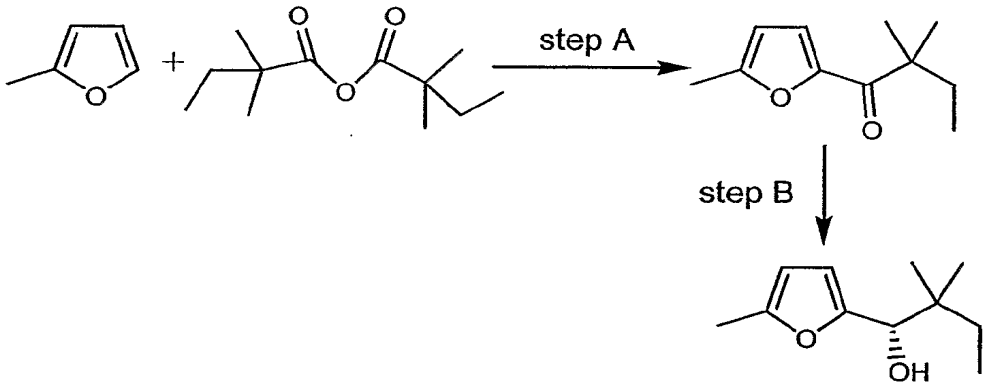
To a solution of 2-methyl furan (1.72g) in ether was added BuLi (8.38mL) at -78^0C and stirred at room temperature for half an hour. The reaction mixture again cooled to -78^0C and quenched with cyclopropyl amide **1** and stirred for two hours at -78^0C and slowly warmed to room temperature. The reaction mixture stirred for three hours at room temperature and quenched with the addition of saturated ammonium chloride solution. The mixture was taken to a separatory funnel, washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent

afforded the crude ketone, which was purified by using column chromatography to afford the ketone 3.0g (87%) as a pale yellow oil.

Step B

To a solution of ketone (1.0g) from Step A above in THF (5.0mL) at 0^0C was added *R*-methyl oxazoborolidine (1.2Ml, 1M in toluene) dropwise followed by addition of a solution of borane complexed with dimethyl sulfide (1.85mL, 2M in THF). The reaction mixture was stirred for 30 minutes at 0^0C and than at room temperature for one hour. The reaction mixture was cooled to 0^0C and MeOH was added carefully. The mixture was stirred for 20 minutes and was concentrated under reduced pressure. The residue was extracted with ether, washed with water, 1M HCl (10mL), saturated sodium bicarbonate (10.0mL) water and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and removal of solvent afforded the crude alcohol which was purified by silica gel chromatography to afford the pure alcohol 0.91g (91%) as yellow oil.

PREPARATIVE EXAMPLES 602



Step A

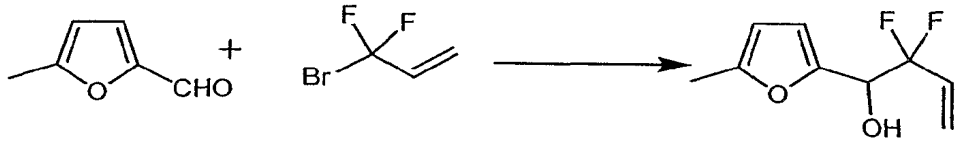
An equimolar mixture of 2-methylfuran (1.0g) and anhydride (2.6g) was mixed with $SnCl_4$ (0.05mL) and heated at 100^0C for 3 hours. After cooling the reaction mixture, water (10mL) was added, followed by saturated sodium carbonate solution until it becomes alkaline. The reaction mixture was extracted with ether several times and the combined ether layer was washed with water, brine and dried over anhydrous sodium sulfate. Filtration and removal of solvent afforded the crude ketone, which was

purified by using silica gel chromatography to afford the ketone 0.9g (43%) as a yellow oil.

Step B

The title alcohol was obtained following a similar procedure set forth in Preparative Example 601.

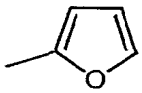
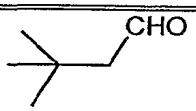
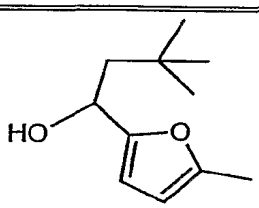
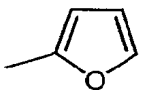
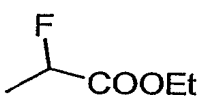
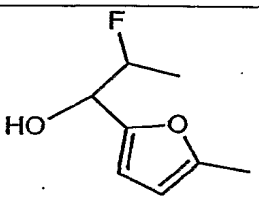
PREPARATIVE EXAMPLES 603

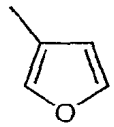
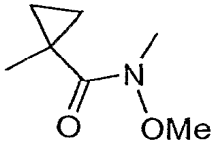
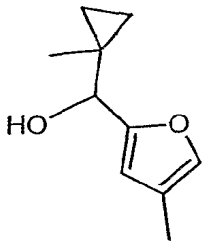
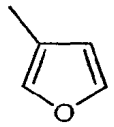
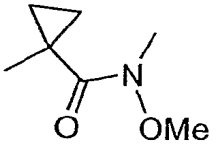
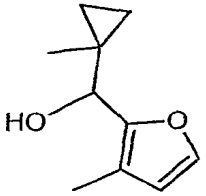
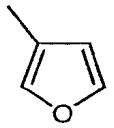
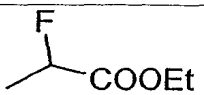
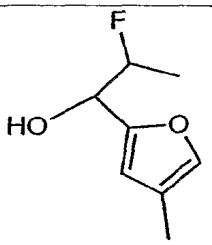
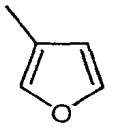
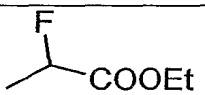
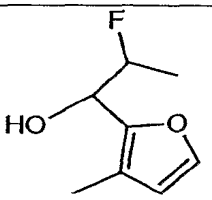
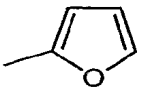
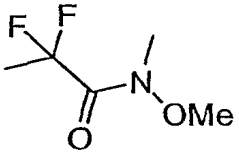
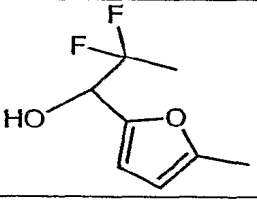
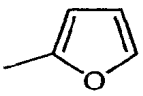
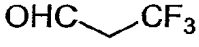
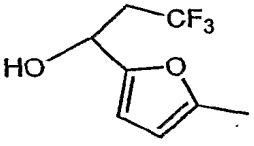


To a solution of 5-methyl furan-2-aldehyde (1.0g) and 3-bromo-3,3-difluoropropene (2.24g) in DMF (30mL) was added indium powder (1.66g) and lithium iodide (50.0mg). The reaction mixture was stirred over night, diluted with water and extracted with ether. The ether layer was washed with water, brine and purified by silica gel chromatography to afford the pure alcohol 2.8g (92%).

PREPARATIVE EXAMPLES 604-611

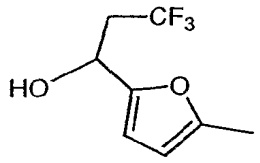
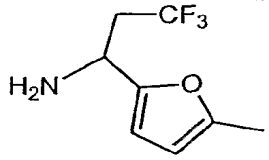
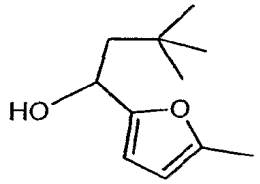
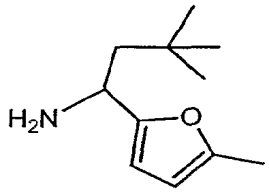
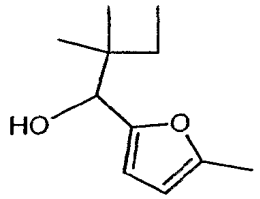
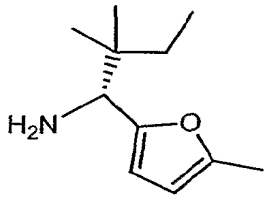
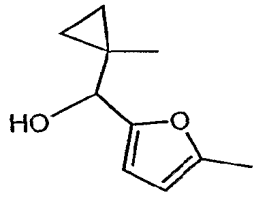
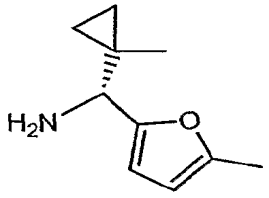
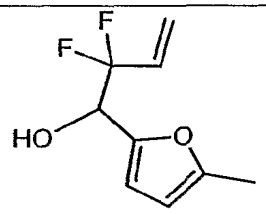
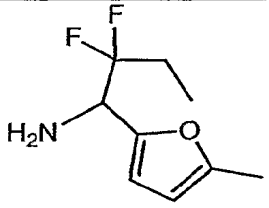
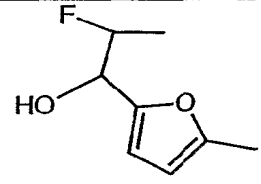
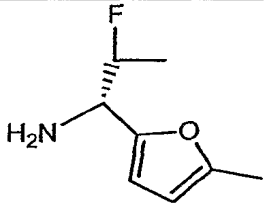
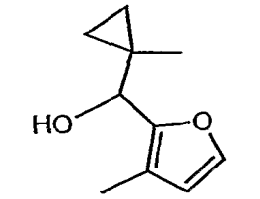
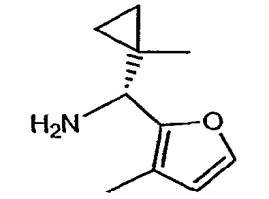
Following a similar procedure set forth in Preparative Example 13.25 of WO 02/083624 published October 24, 2002, or Preparative Example 601, the following Alcohols were prepared.

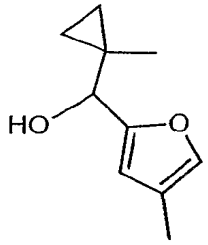
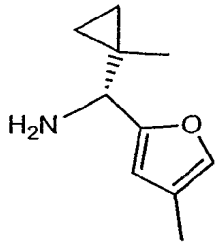
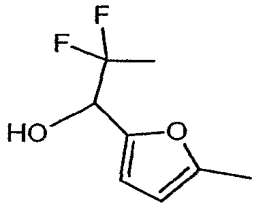
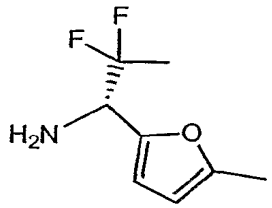
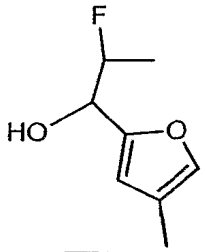
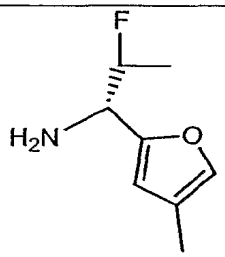
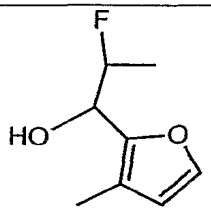
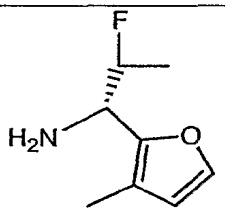
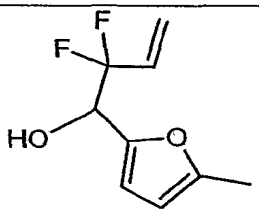
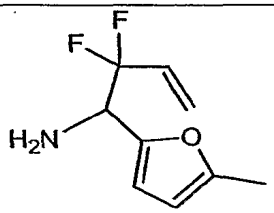
Prep Ex	Furan	Electrophile	Alcohol	Yield
604				86%
605				69%

606				84%
607				82%
608				60%
609				65%
610				82%
611				89%

PREPARATIVE EXAMPLES 620-631

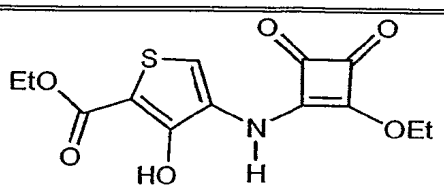
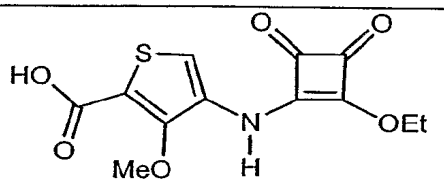
Following a similar procedure set forth in Preparative Examples 13.25 the following Amines were prepared from the corresponding Alcohols.

Prep Ex	ALCOHOL	AMINE	YIELD
620			28%
621			58%
622			69%
623			81%
624			82%
625			45%
626			57%

627			58%
628			54%
629			53%
630			50%
631			82%

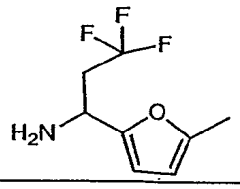
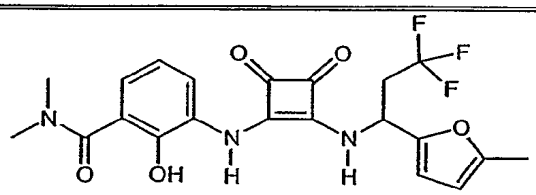
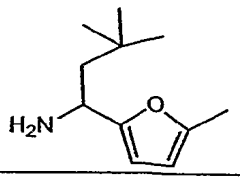
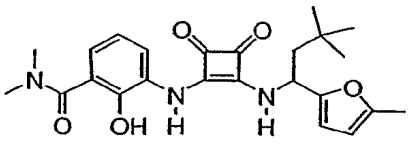
PREPARATIVE EXAMPLE 640-641

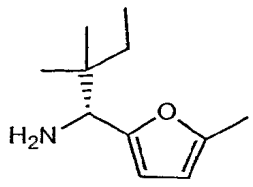
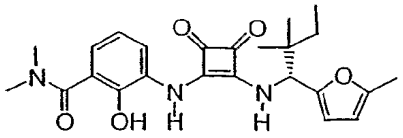
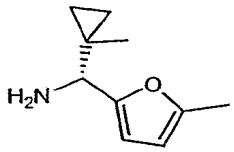
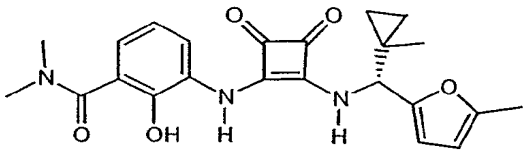
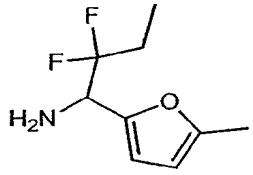
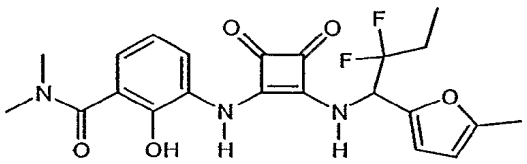
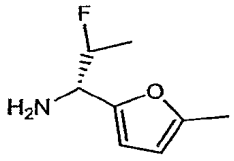
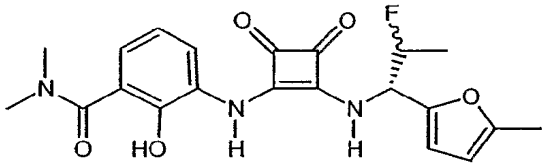
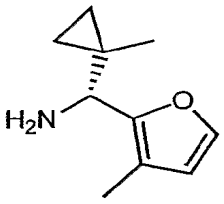
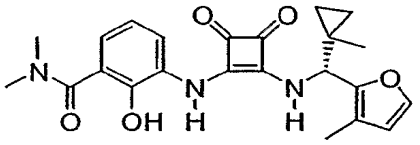
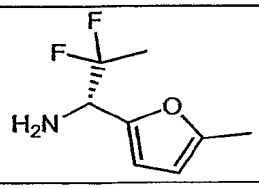
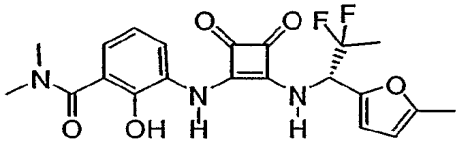
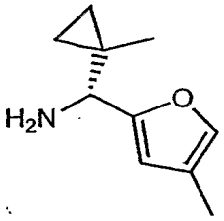
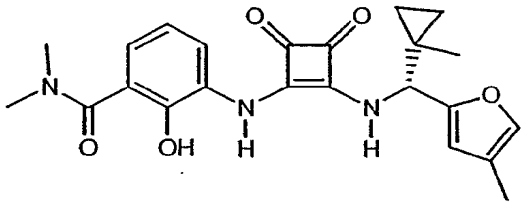
Following the procedures set forth in Preparative Example 19 of WO 02/083624, published October 24, 2002, but using the amine from the Preparative Example indicated in the Table below, the cyclobutenedione intermediates were obtained.

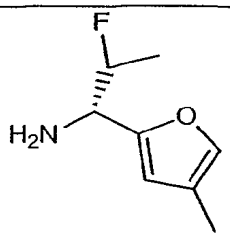
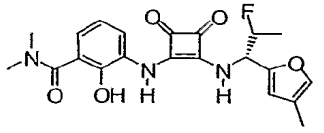
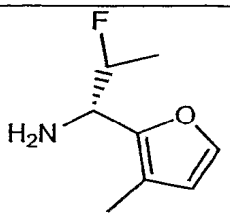
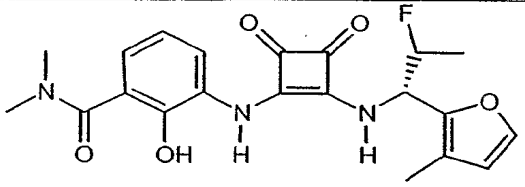
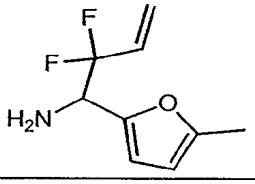
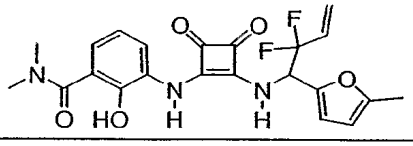
Prep Ex.	Amine from Prep Ex.	Product	1. Yield (%) 2. MH^+
640	600 Step B		1. 60% 2. 138
641	600 Step D		1. 66 2. 138

EXAMPLES 1200-1211

Following the procedure set forth in Example 261 of WO 02/083624, published October 24, 2002, but using the commercially available amine or the prepared amine from the Preparative Example indicated in the table below, the following cyclobutenedione products were obtained.

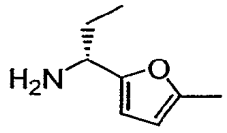
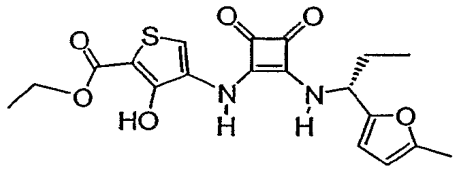
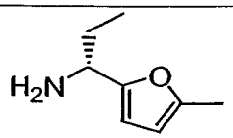
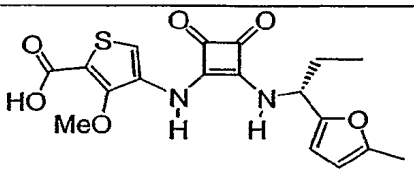
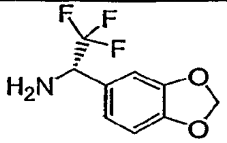
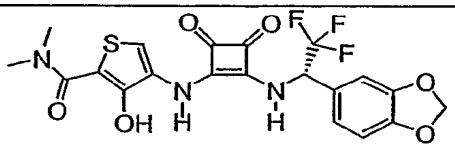
Ex.	Amine	Product	1.Yield (%) 2. MH^+ 3. mp (°C)
1200			1. 61.3 2. 451.4 3. 108.6
1201			1. 54 2. 439.5 3. 117.8

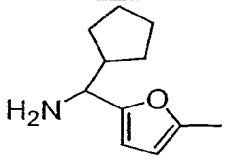
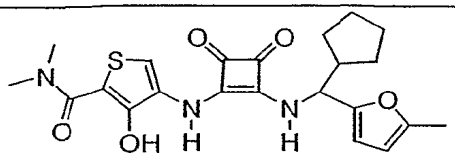
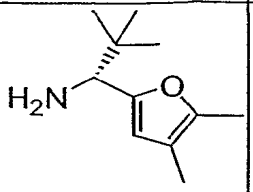
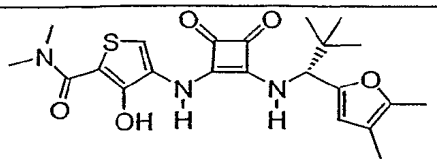
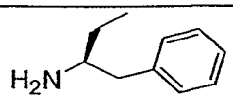
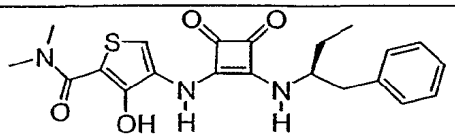
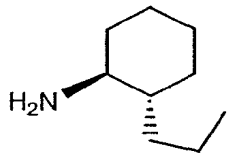
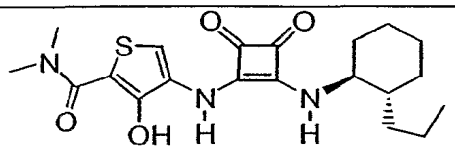
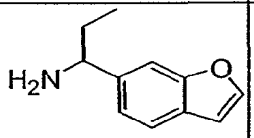
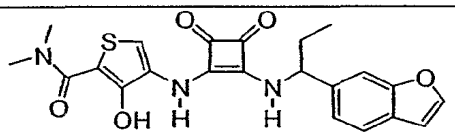
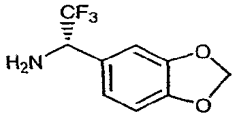
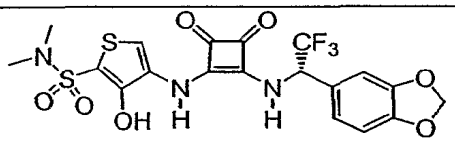
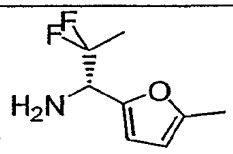
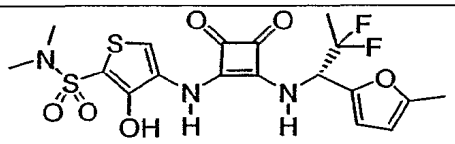
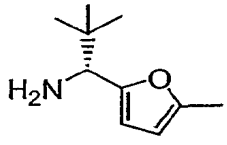
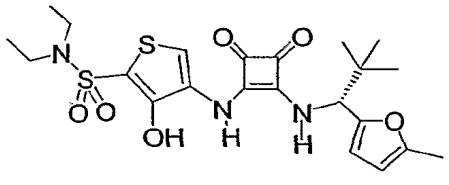
1202			1. 80 2. 439.5 3. 128-131.8
1203			1. 75 2. 423.4 3. 118-119
1204			1. 74 2. 447.4 3. 108-111
1205			1. 42 2. 415.42 3. 136-140
1206			1. 46 2. 423.4 3. 114-117
1207			1. 35 2. 433.1 3. 123-128
1208			1. 42 2. 423.4 3. 118-121

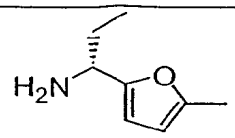
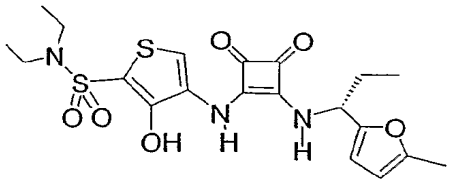
1209			1. 51 2. 415.4 3. 112-117
1210			1. 44 2. 415.4% 3. 115-120
1211			1. 48 2. 445.4 3. 105-110

EXAMPLES 1300-1311

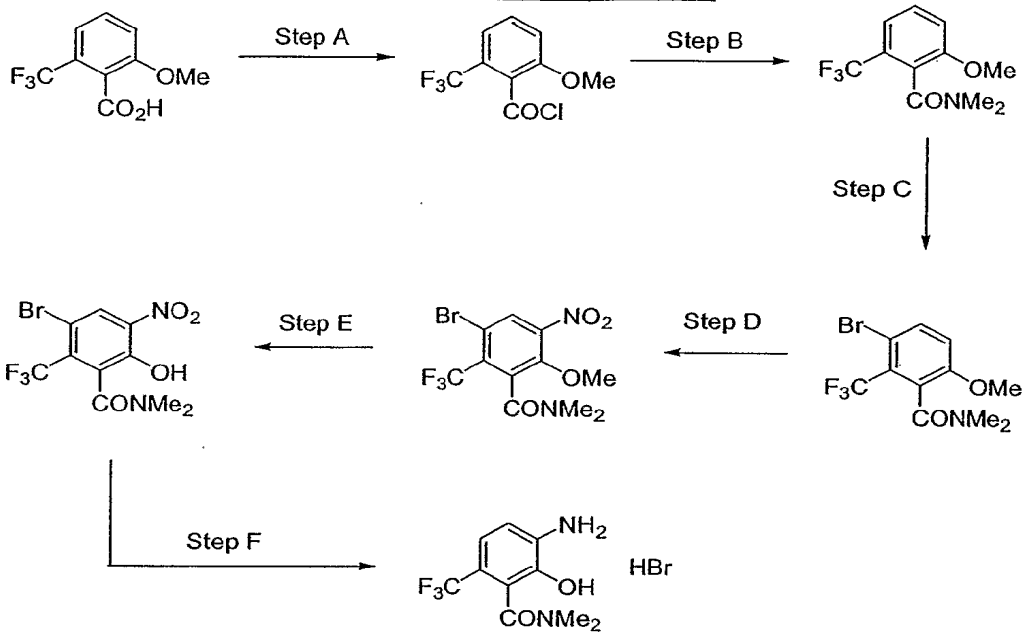
Following the procedure set forth in Example 261, of WO 02/083624, published October 24, 2002, but using the commercially available amine in the table below and the cyclobutenedione intermediate from the Preparative Example indicated, the following cyclobutenedione products were obtained. Preparative Example 23.9 is in WO 02/083624, published October 24, 2002.

Ex.	Amine	Prep. Ex.	Product	1.Yield (%) 2. MH^+ 3. mp (°C)
1300		640		1. 35% 2. 390.4 3. 100
1301		641		1.78% 2. 390.4 3. 130
1302		23.9		1. 48% 2. 483.4 3. 116

1303		23.9		1. 46% 2. 443.5 3. 106
1304		23.9		1. 40% 2. 445.54 3. 102
1305		23.9		1. 51% 2. 413.4 3. 98
1306		23.9		1.78% 2. 405.5 3. 246
1307		23.9		1. 83% 2. 439.5 3. 129
1308		23.15A		1. 11% 2. 519.47 3. 123
1309		23.15A		1. 47% 2. 475 3. 113
1310		640		1. 55% 2. 496.1 3. 123-125

1311		640		1. 74% 2. 468.1 3. 116-118

Preparative Example 1001



Step A

Oxalyl chloride (3 mL, 34.27 mmol) was added dropwise to a mixture of 2-methoxy-6-(trifluoromethyl)benzoic acid (1.5 g, 6.81 mmol) (prepared according to known method, see: EP0897904B1), *N*,*N*-dimethylformamide (0.3 mL), and dichloromethane (40 mL) with stirring at rt. The reaction mixture was stirred overnight. Evaporation of solvent and excess oxalyl chloride and drying under vacuum afforded 2-methoxy-6-(trifluoromethyl)benzoyl chloride as a solid, which was used without purification.

Step B

A solution of 2-methoxy-6-(trifluoromethyl)benzoyl chloride (ca. 6.81 mmol) from Step A above in dichloromethane (20 mL) was added dropwise to a mixture of 4-(dimethylamino)pyridine (42 mg, 0.34 mmol), triethylamine (2.8 mL, 20.09 mmol), and 2 M dimethylamine solution in tetrahydrofuran (7 mL, 14 mmol), and dichloromethane

(30 mL) with stirring at rt. The reaction mixture was stirred overnight. A mixture of dichloromethane and water was added. The organic phase was separated, washed with 1N HCl solution, water, and saturated sodium bicarbonate solution and concentrated. The residue was purified by column chromatography (ethyl acetate:hexanes, 3:1 v/v) to give the product as a white solid (1.24 g, 74% over two steps).

Step C

A mixture of the amide from Step B above (1.8 g, 7.28 mmol), carbon tetrachloride (25 mL), and iron powder (305 mg, 5.46 mmol) was cooled to 0 °C. Bromine (0.94 mL, 18.34 mmol) was added dropwise with stirring. After addition, the mixture was stirred at rt for 1 h and at 50 °C for 3 h. The mixture was cooled to rt, diluted with dichloromethane, and slowly poured to a cold 10% $NaHSO_3$ solution. After stirring at rt for 0.5 h, the organic layer was separated and concentrated to give the product as a white solid (2.26 g, 95%).

Step D

Concentrated sulfuric acid (10 mL) was added dropwise to a flask charged with the bromide from Step C above (600 mg, 1.84 mmol) at 0 °C with stirring. A mixture of nitric acid (0.2 mL, 4.76 mmol) and concentrated sulfuric acid (0.3 mL) was then added dropwise. After addition, the mixture was stirred at rt for 3 h. The mixture was added to ice-water, neutralized with 15% NaOH solution to pH 7, and extracted with dichloromethane. The organic layer was concentrated to give the product as a white solid (621 mg, 91%). mp 92 °C, *m/e* 371 (MH^+).

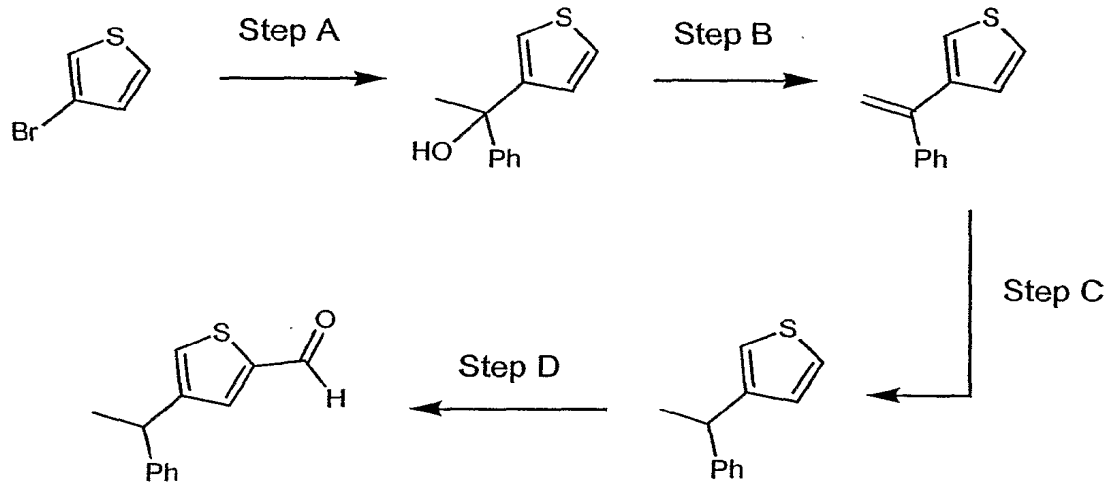
Step E

A solution of the compound from Step D above (1.2 g, 3.23 mmol) in dichloromethane (50 mL) was cooled to –75 °C. 1 M BBr_3 solution in dichloromethane (7.5 mL, 7.5 mmol) was added dropwise with stirring. The mixture was stirred at –75 °C for 2 h. The mixture was added to ice-water. After stirring at rt for 0.5 h, the mixture was extracted with dichloromethane. The organic was concentrated and the residue was purified by column chromatography (dichloromethane-methanol, 9:1 v/v) to give the product as a yellow solid (1.05 g, 91%). *m/e* 357 (MH^+).

Step F

A mixture of the compound from Step E above (1.08 g, 3.02 mmol), methanol (30 mL), and 10% Pd-C (250 mg) was subjected to hydrogenation at 50 psi at rt for 6 h. The mixture was filtered through a layer of Celite. The filtrate was concentrated to give the title compound as a pale yellow solid (930 mg, 96%). mp 132 °C, *m/e* 249.

Preparative Example 1002



Step A

To a cooled (-70°C) etherial (45 mL dry) solution of 3-bromothiophene (3.8 mL) was added BuLi (30 mL of 1.6M in hexane) dropwise, and the mixture was stirred at -70°C for 20 min. Acetophenone (4.6 mL) in ether (6 mL) was added dropwise with stirring at -70°C. After 3 hrs, the mixture was warmed to RT and sat. NH_4Cl (aq) was added and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound which was used in Step B without further purification.

Step B

The crude product from Step A above was stirred with oxalic acid (0.375 g) at 70°C under reduced pressure for 3 hr, then cooled to RT and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the product as a pale yellow liquid (5.7 g, 78% for Steps A-B).

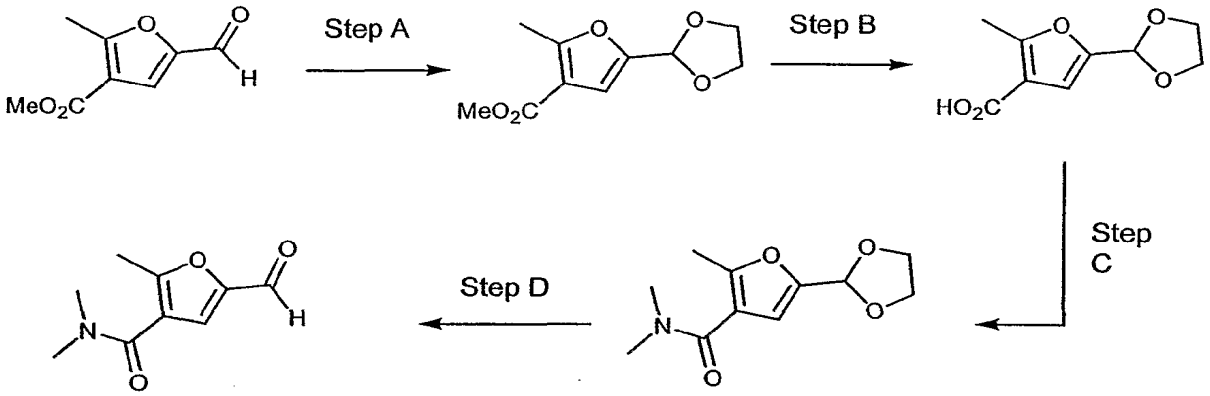
Step C

To the product from Step B above (4.2 g) diluted with dichloromethane (30 mL) and containing triethylsilane (6 mL) was added TFA (3 mL) in dichloromethane (7.5 mL). After stirring at RT for 10 min, the mixture was concentrated in vacuo to give the product as a colorless liquid (4.61 g, 80%).

Step D

To an etherial (3.5 mL dry) solution of the thiophene product (1.5 g) from Step C above was added BuLi (3.2 mL of 2.5M), and the mixture was heated at reflux for 15 min, cooled to RT, and DMF (0.8 mL) in ether (3.5 mL) was added dropwise. After stirring for 30 min, sat. NH_4Cl (aq) was added and the mixture was extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give the title compound (1.71 g, 98%).

Preparative Example 1003



Step A

The aldehyde (0.50 g) was combined with ethylene glycol (1 mL), benzene (40 mL) and pTSA monohydrate (30 mg) and stirred at reflux for 20 hr. Cool to room temperature, add EtOAc and sat. $NaHCO_3$ (aq) solution, separate the organic phase, concentrate in vacuo, and purify by silica gel chromatography (EtOAc-Hex, 1:4) to give a colorless liquid (60 mg)

Step B

The product from Step A above (0.607 g) was stirred at 45°C overnight with 1N NaOH (aq), then cooled to room temperature, acidified with 3N HCl and extracted with EtOAc. Washing with brine and concentration in vacuo gave a solid (5.0 g).

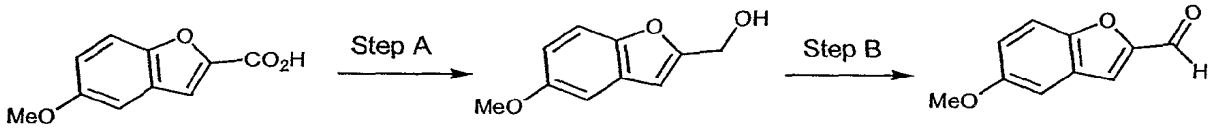
Step C

Following a similar procedure as that used in Preparative Example 1, except using the product from Step B above and dimethylamine in THF (2M), the product was obtained (1.21g crude).

Step D

The product from Step C above was dissolved in THF and stirred with 0.3N HCl (aq) and stirred at RT for 4 hr. Concentration in vacuo gave a pale yellow oil (1.1 g, 67%).

Preparative Example 1004



Step A

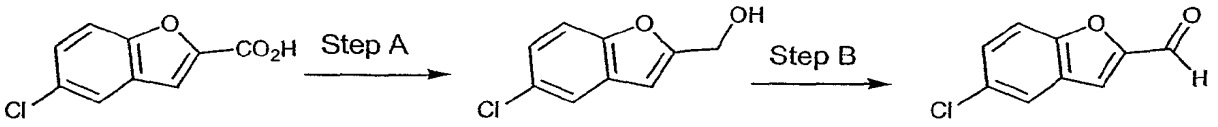
To a cooled (-78°C) solution of methoxybenzofuran-2-carboxylic acid (1 g) was added DIBAL (30 mL, 1M in THF). After stirring for 20 min, the mixture was warmed to RT and stirred for 4 hr, then poured into sat. NH4Cl (aq) (35 mL). After stirring at RT for 20 min, 6M HCl (aq) was added and the mixture was extracted with EtOAc, the organic phase dried and then concentrated in vacuo. Purification by silica gel chromatography (EtOAc-hexane, 3:7) afforded the alcohol as a solid (0.4 g, 97%).

Step B

A mixture of the product from Step A above (0.9 g), EtOAc (50 mL) and MnO2 (5.2 g) was stirred at RT for 22 h, then filtered and concentrated in vacuo. The solid was redissolved in EtOAc (50 mL), MnO2 (5.2 g) was added and the mixture was

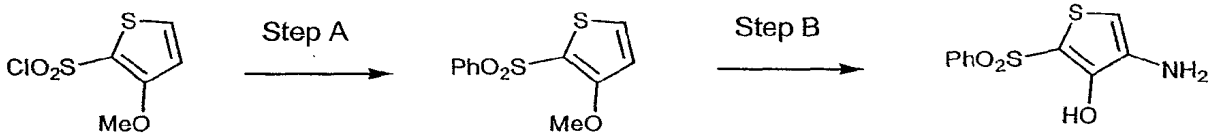
stirred for 4 additional hrs. Filtration, concentration and silica gel purification (EtOAc-Hexane, 1:3) gave the title compound as a solid (0.60 g, 67%).

Preparative Example 1005



Following a similar procedure as that detailed in Preparative Example 1004, except using 5-chlorobenzofuran-2-carboxylic acid (1.5 g), the title compound was obtained (solid, 0.31 g, 24%).

Preparative Example 1006



Step A

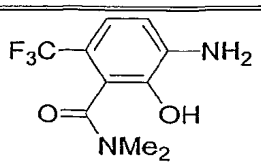
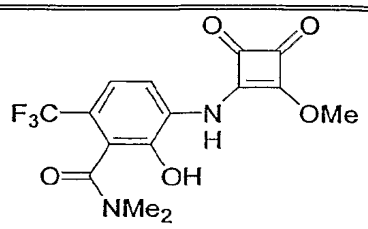
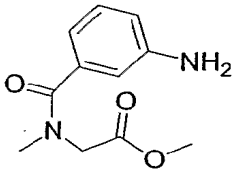
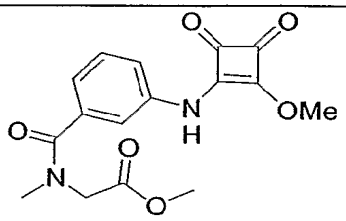
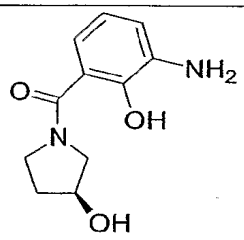
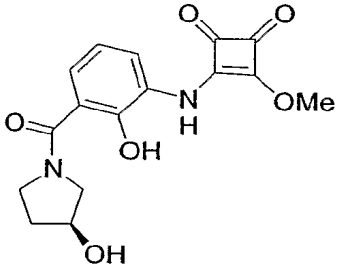
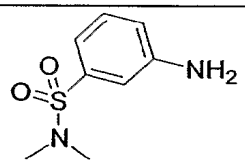
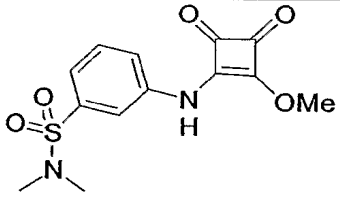
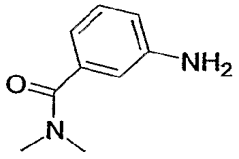
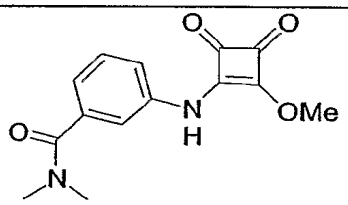
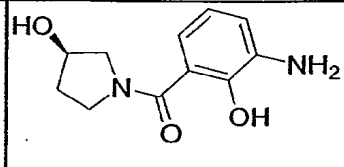
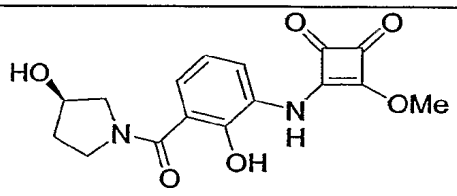
The sulfonyl chloride from Preparative Example 13.29 Step A (1.5 g) was stirred with AlCl3 and benzene for 15 min at 20 °C. Treatment with NaOH, extraction with Et_2O, concentration in vacuo, and purification by column chromatography (silica, hexane-EtOAc, 5:2) gave the phenylsulfone (1.5g, 84%, MH^+ = 255).

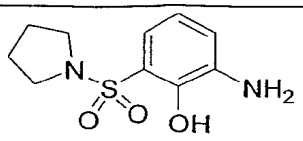
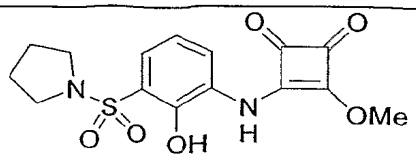
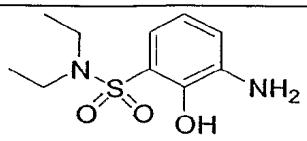
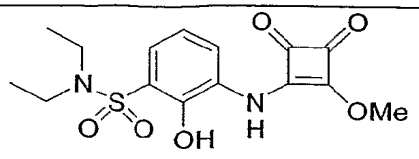
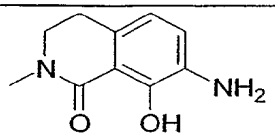
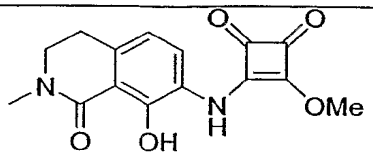
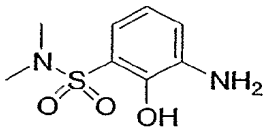
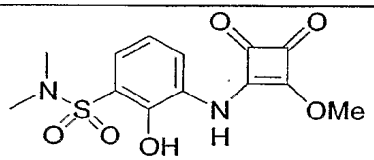
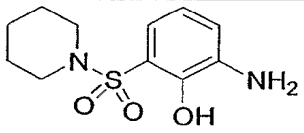
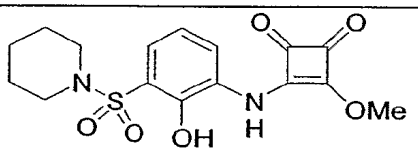
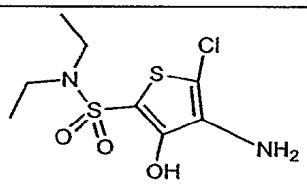
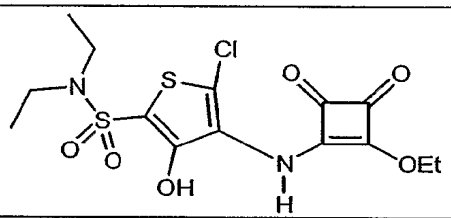
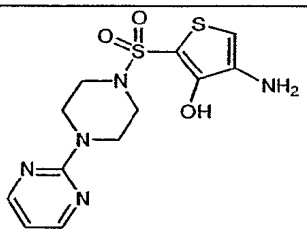
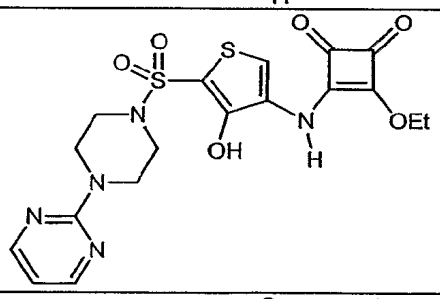
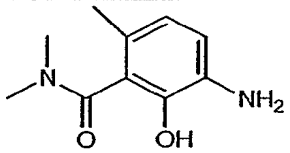
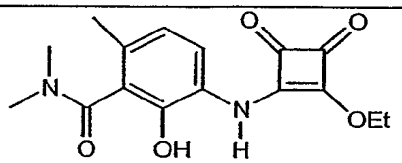
Step B

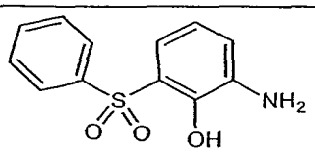
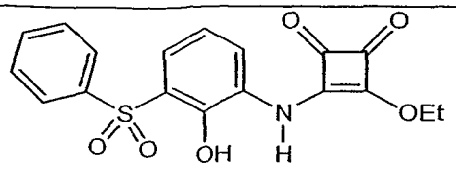
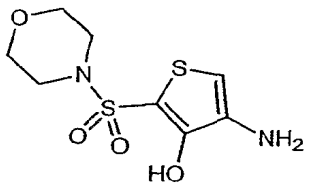
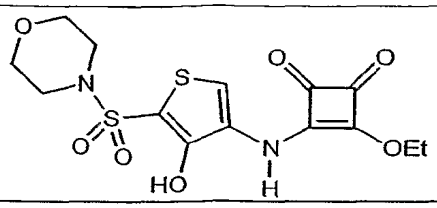
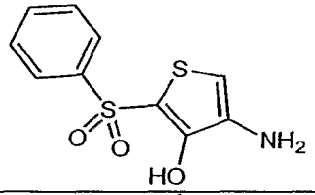
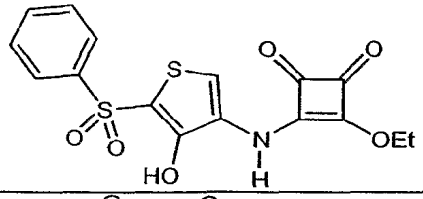
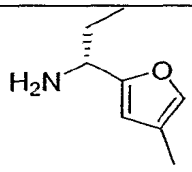
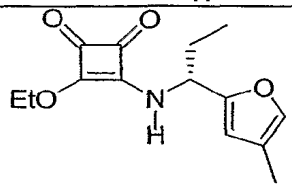
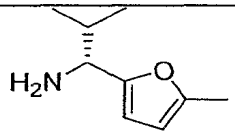
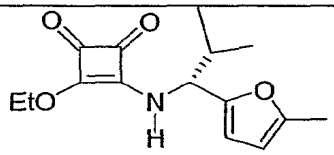
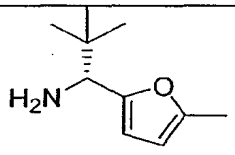
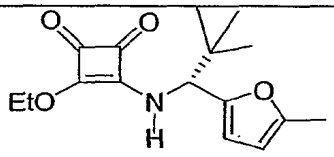
Following similar procedures as those used in Preparative Example 13.29 Steps C-G, except using the sulfone from Step A above, the title compound was prepared (0.04 g, 27%, MH^+ = 256).

Preparative Example 1007-1029

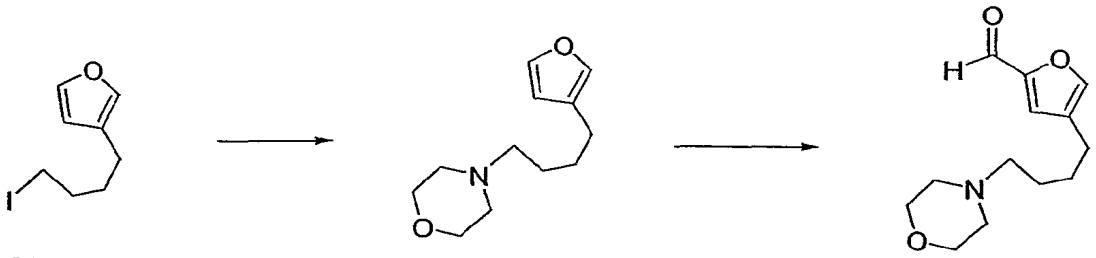
Following a similar procedure set forth in Preparative Example 19.1 of WO 02/083624, published October 24, 2002, or Preparative Example 19.2, but using the Amine (Anilines) listed in the Table below, the following squarate intermediates were prepared.

Example	Amine/Aniline	Product	1.Yield (%) 2. $(M+1)^+$
1007			1. 95% 2. 359
1008			1. 99% 2. 333
1009			1. 99% 2. 333
1010			1. 99% 2. 311
1011			1. 99% 2. 275
1012			1. 99% 2. 333

1013			1. 72% 2. 353.0
1014			1. 60% 2. 355.1
1015			1. 70% 2. 303.1
1016			1. 45% 2. 327.0
1017			1. 70% 2. 367.0
1019			1. 32% 2. 409
1020			1. 48% 2. 466
1021			1. ~60% (crude)

1022			1. 21%
1023			1. 45% 2. 389
1024			1. 30% 2. 380
1027			1. 44% 2. 264
1028			1. 56% 2. 278
1029			1. 47% 2. 292

Preparative Example 1030



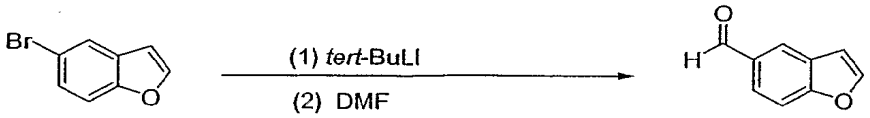
Step A

The product of Preparative Example 34.18 Step B (2 g, 8 mmol) was stirred with morpholine (0.9 mL, 10.29 mmol) and K2CO3 (2.2 g, 15.9 mmol) in 50 mL of acetone at RT to obtain the morpholinobutylfuran derivative (1.22 g,73%).

Step B

Following a similar procedure as in Preparative Example 34.18 Step D, but using the product (1.2 g) from Step A above, the title aldehyde was prepared (0.9 g,66%, 1:0.7 regioisomeric mixture).

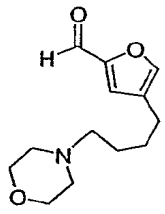
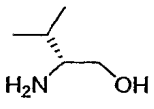
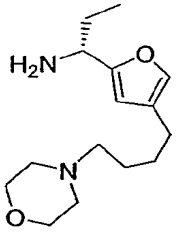
Preparative Example 1031

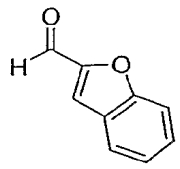
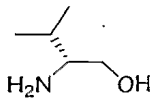
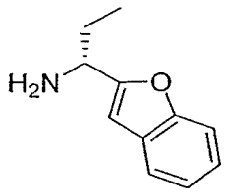
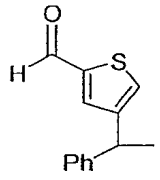
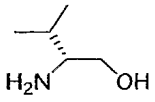
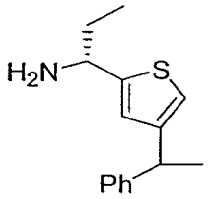
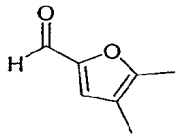
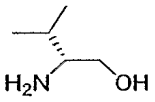
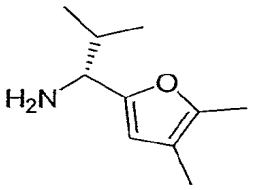
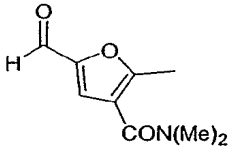
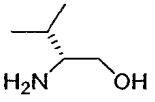
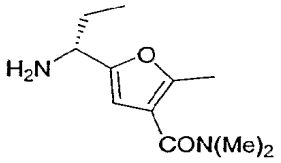
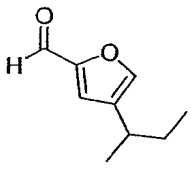
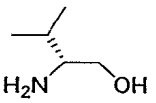
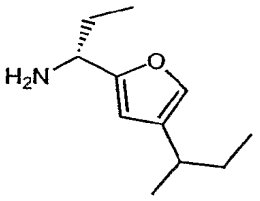
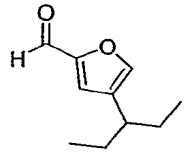
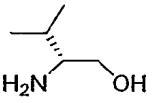
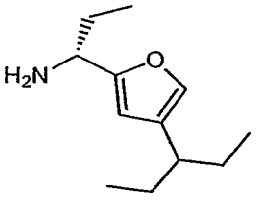
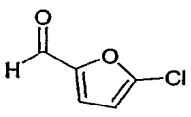
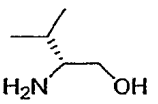
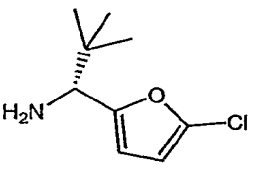


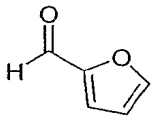
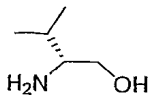
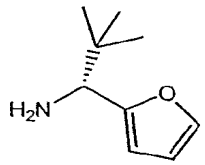
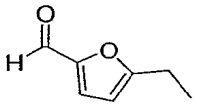
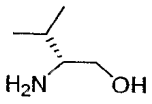
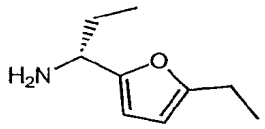
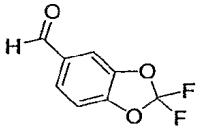
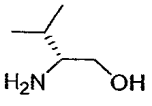
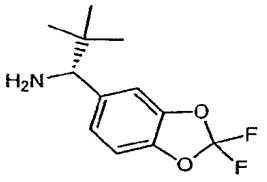
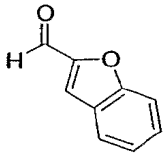
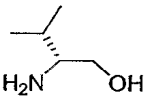
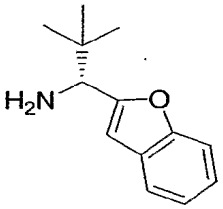
A solution of 5-bromobenzofuran (950 mg, 4.82 mmol) in anhydrous ether (12 mL) was cooled to –78 °C. 1.7 M *tert*-BuLi solution in pentane (6 ml, 10.2 mmol) was added dropwise under argon. After addition, the mixture was stirred at –78 °C for 20 min, followed by addition of a mixture of DMF (0.8 mL) and ether (1 mL). The mixture was allowed to warm to rt and stirred for 0.5 h. Ethyl acetate was added. The mixture was poured to saturated ammonium chloride solution. The organic layer was separated and concentrated. The residue was purified by column chromatography (ethyl acetate-hexanes, 1:5 v/v) to give the title compound as a pale yellow solid (490 mg, 70%).

PREPARATIVE EXAMPLES 1040-1054

Following the procedure set forth in Preparative Example 64 of WO 02/083624, published October 24, 2002, but using the commercially available (or prepared) aldehyde, aminoalcohols, and organolithium reagents in the Table below, the optically pure amine products in the Table below were obtained.

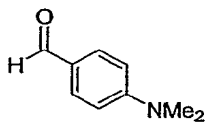
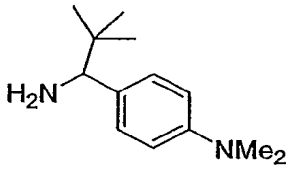
Prep. Ex.	Aldehyde	Amino Alcohol	Organo-lithium	Product	1.Yield (%) 2. $(M+1)^+$
1040			EtLi		1. 24% 2. 267

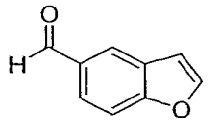
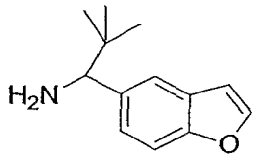
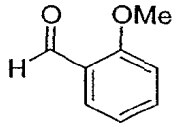
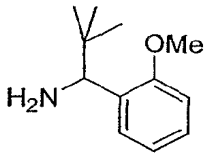
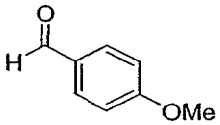
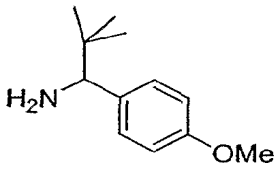
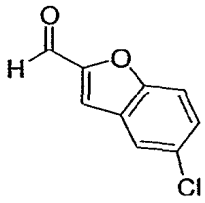
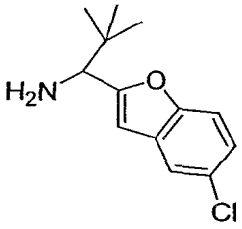
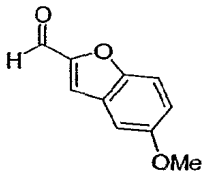
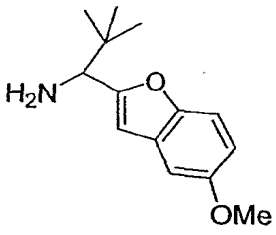
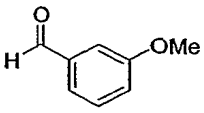
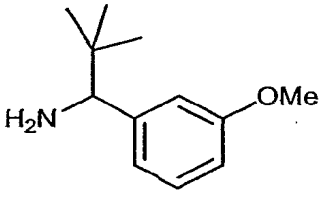
1041			EtLi		1. 94% 2. 176 (m/e)
1042			EtLi		1. 67% 2. 229 (M-16)
1043			i-PrLi		1. 60% 2. 151 [M-16]
1044			EtLi		1. 74% 2. 194 (M-16)
1045			EtLi		1. 33% 2. 165 [M-NH2]$^+$
1046			EtLi		1. 31 2. 179 [M-NH2]$^+$
1047			t-BuLi		1. 31% 2. 188

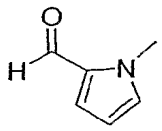
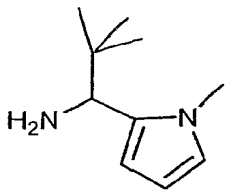
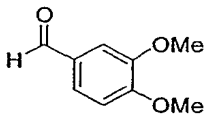
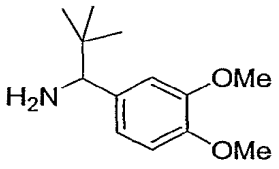
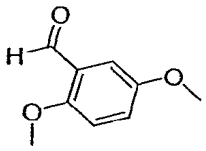
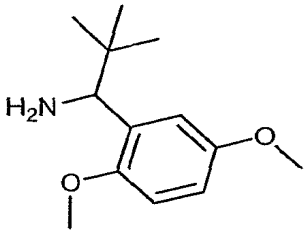
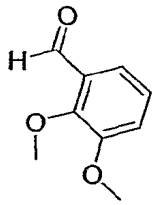
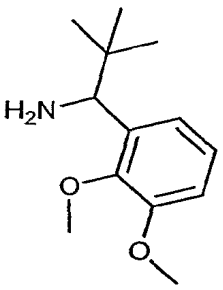
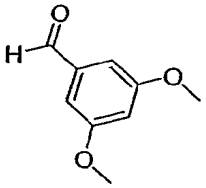
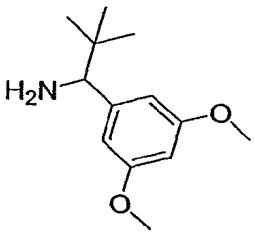
1048			t-BuLi		1. 10% 2. 154
1049			EtLi		1. 73% 2. 137 [M-NH2]$^+$
1051			t-BuLi		1. 17%
1054			t-BuLi		1. 79% 2. 151 (M-16)

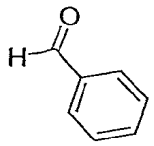
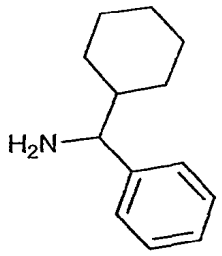
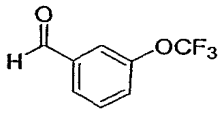
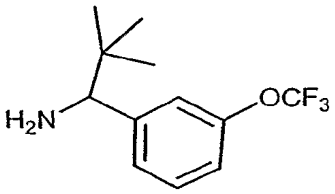
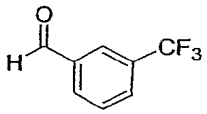
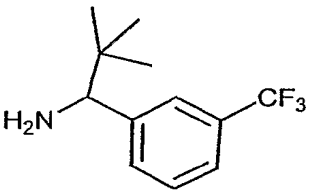
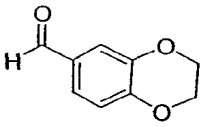
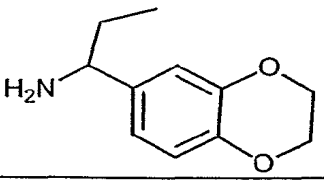
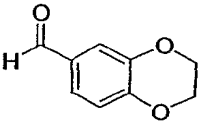
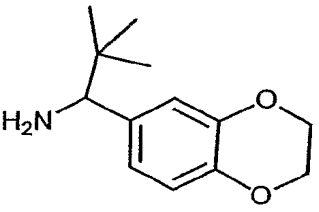
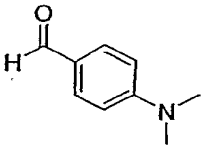
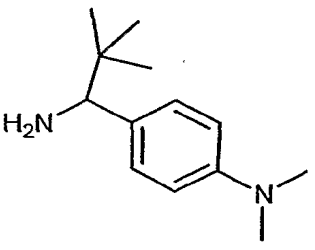
PREPARATIVE EXAMPLES 1100-1126

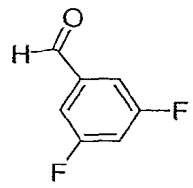
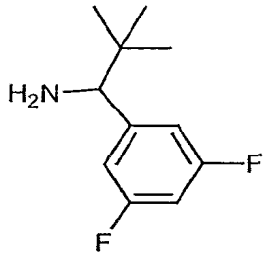
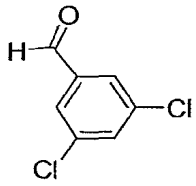
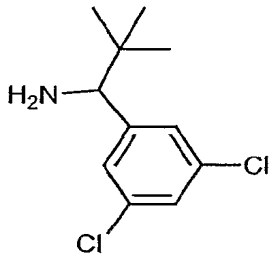
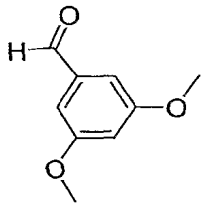
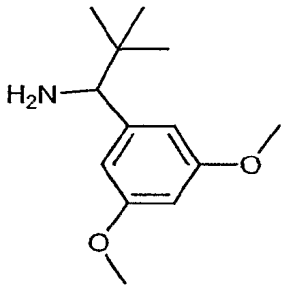
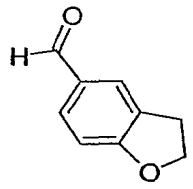
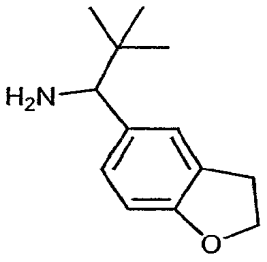
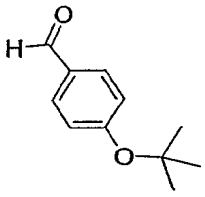
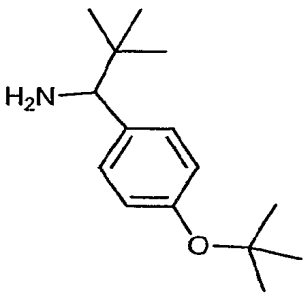
Following the procedure set forth in Preparative Example 34 of WO 02/083624, published October 24, 2002, but using the commercially available aldehydes and Grignard/Organolithium reagents listed in the Table below, the amine products were obtained.

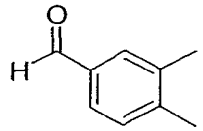
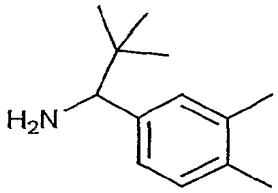
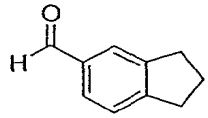
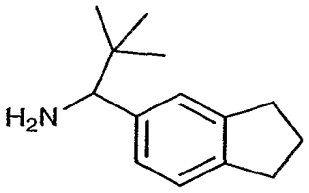
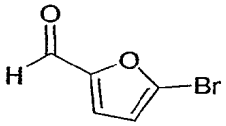
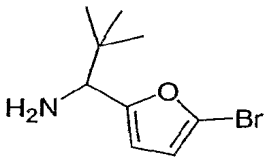
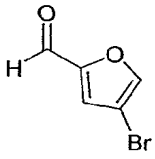
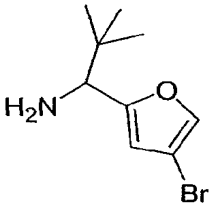
Prep. Ex.	Aldehyde	Organo-metallic Reagent	Product	1.Yield (%) 2. (M+1)$^+$
1100		t-BuLi		1. 83% 2. 190 (M-16)

1101		t-BuLi		1. 46% 2. 204
1102		t-BuLi		1. 48% 2. 194
1103		t-BuLi		1. 51% 2. 194
1104		t-BuLi		1. 12% 2. 238
1105		t-BuLi		1. 39% 2. 234
1106		t-BuLi		1. 44% 2. 194 (m/e)

1107		t-BuLi		1. 57% 2. 150 (M-16)
1108		t-BuLi		1. 31% 2. 224
1109		t-BuLi		1. 11% 2. 224
1110		t-BuLi		1. 57% 2. 224
1111		t-BuLi		1. 21% 2. 224

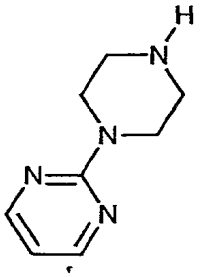
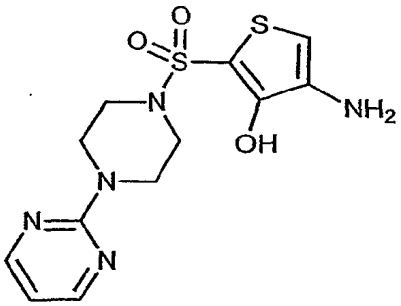
1112		c-Pentyl-Li		1. 58% 2. 190
1113		t-BuLi		1. 20% 2. 248
1114		t-BuLi		1. 24% 2. 232
1115		EtLi		1. 32% 2. 177 (M-NH2)
1116		t-BuLi		1. 26% 2. 205 (M-NH2)
1117		t-BuLi		1. 50% 2. 190 (M-NH2)

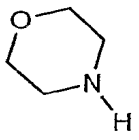
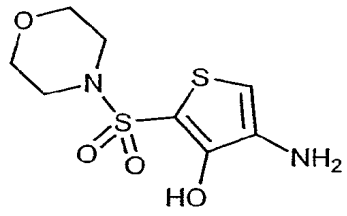
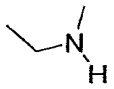
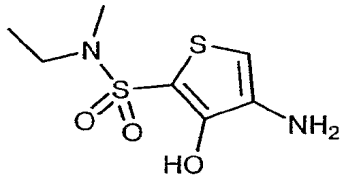
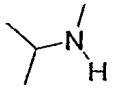
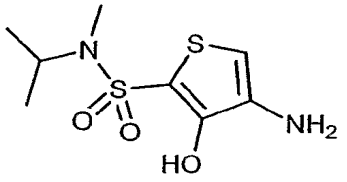
1118		t-BuLi		1. 29% 2. 200
1119		t-BuLi		1. 28% 2. 232
1120		t-BuLi		1. 76% 2. 224
1121		t-BuLi		1. 40% 2. 206
1122		t-BuLi		1. 38% 2. 236

1123		t-BuLi		1. 70% 2. 192
1124		t-BuLi		1. 81% 2. 204
1125		t-BuLi		33%
1126		t-BuLi		50%

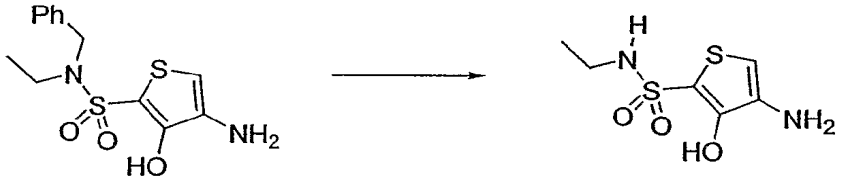
PREPARATIVE EXAMPLES 1200-1203

Following the procedure set forth in Preparative Example 13.29 but using the commercially available amines, the hydroxyaminothiophene products listed in the Table below were obtained.

Prep. Ex.	Amine	Product	1.Yield (%) 2. $(M+1)^+$
1200			1. 3% 2. 342

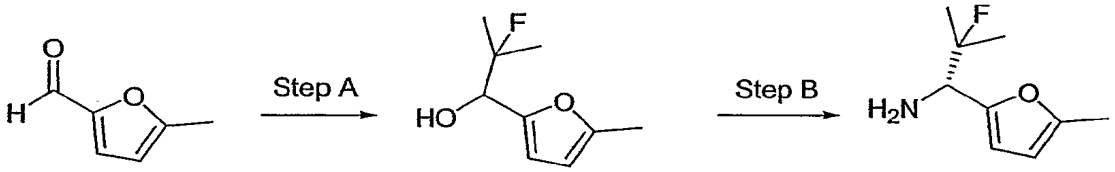
1201			1. 41% 2. 265
1202			1. 17% 2. 237
1203			1. 1%

PREPARATIVE EXAMPLE 1300



The title compound from Preparative Example 13.32 (0.35 g) was treated with concentrated sulfuric acid (3 mL) for 6 hrs, then poured on ice, and the pH adjusted to 4 with NaOH. Extraction with EtOAc, and drying of the organic phase over Na_2SO_4 gave the title compound (159 mg, 64%, MH^+ = 223).

PREPARATIVE EXAMPLE 1301



Step A

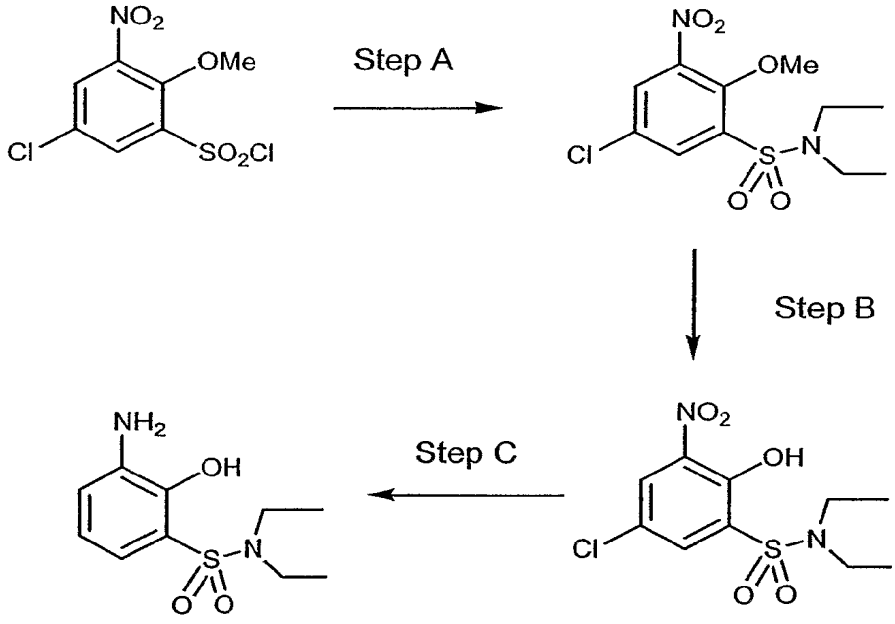
Step A

Following the procedure set forth in Preparative Example 605 but using the commercially available fluoroisopropylester, the alcohol product was obtained (1.2 g, 84%, M-OH = 155).

Step B

Following the procedure set forth in Preparative Example 625 but using the alcohol from Step A above, the amine product was obtained (350 mg, 35%, M-NH2 = 155).

PREPARATIVE EXAMPLE 1302



Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available arylsulfonylchloride (0.15 g) and diethylamine (2.2 eq), the dimethylsulfonamide was obtained (0.12 g, 71%, MH^+ = 323).

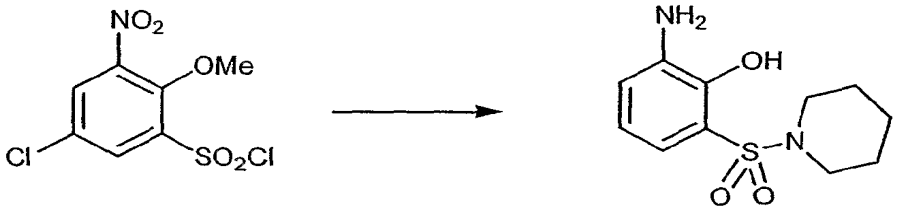
Step B

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step A above (0.12 g), the phenol was obtained (0.112 g, 98%).

Step C

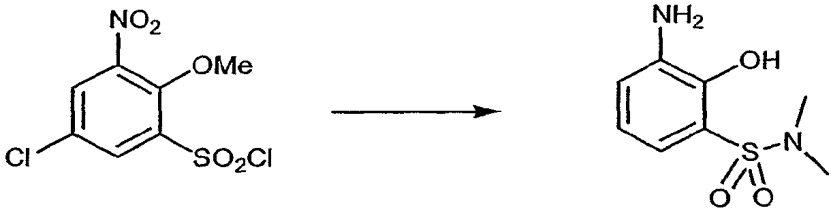
Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (0.112 g), the title compound was obtained (0.1 g, 99%, MH^+ = 245).

PREPARATIVE EXAMPLE 1303



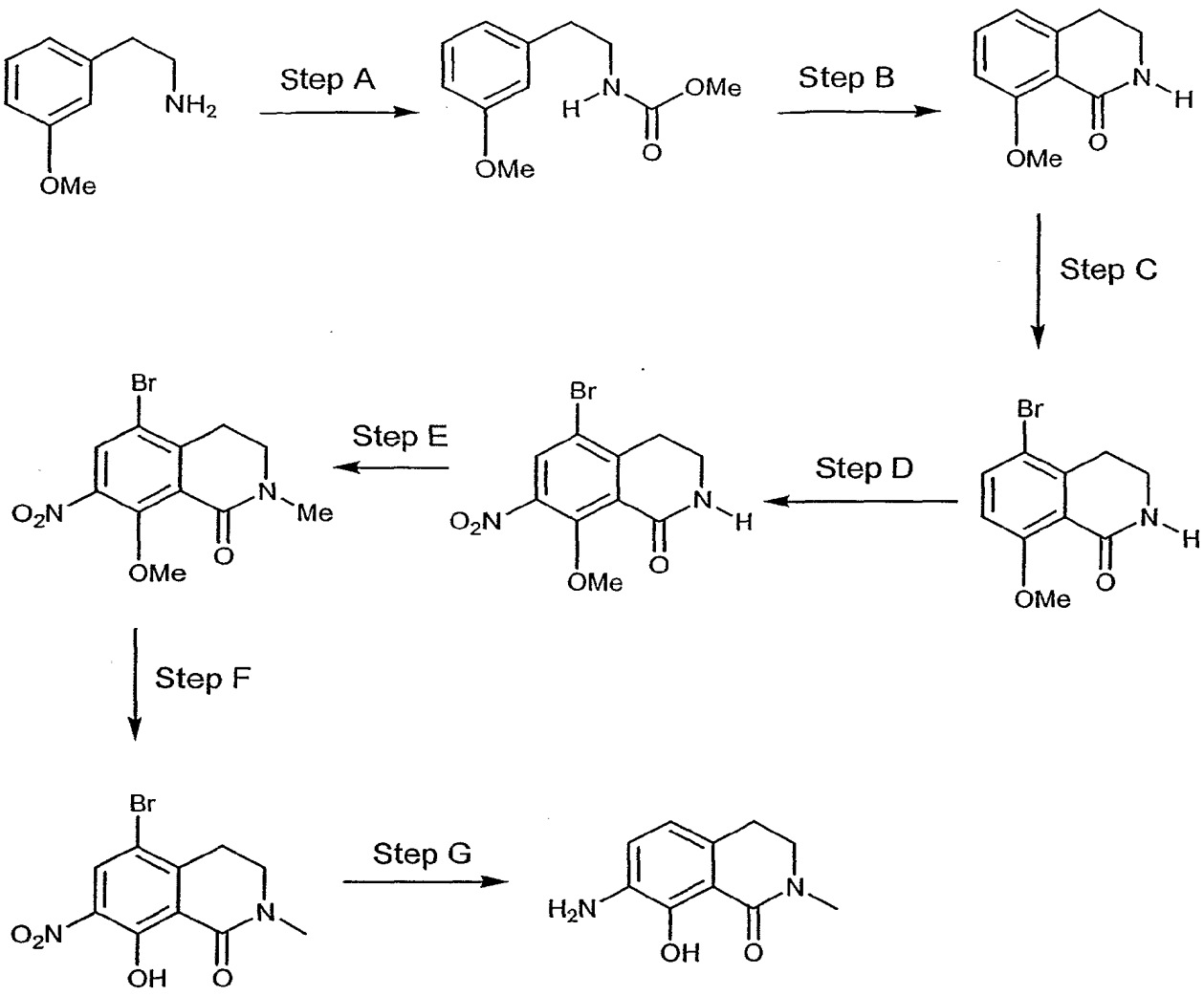
Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using piperidine in Step A (0.078 g) instead of diethylamine, the title compound was obtained (0.070 g, 35%, MH^+ = 257).

PREPARATIVE EXAMPLE 1304



Following a similar procedure as that used in Preparative Example 1302 Steps A-C, except using dimethylamine (2*M* in THF) in Step A instead of diethylamine, the title compound was obtained (1.92g, 72%, MH^+ = 217).

PREPARATIVE EXAMPLE 1305



Step A

Following a similar procedure as that used in Preparative Example 1302 Step A, except using the phenethylamine indicated (4.99 g), the product was obtained (5.96 g, 86%, MH^+ = 210).

Step B

The compound from Step A above (5.0 g) was added to 30 g of PPA at 150°C and the resulting mixture stirred for 20 min, before being poured on ice and extracted with dichloromethane. The organic phase was dried over MgSO4, concentrated in vacuo and purified by silica gel chromatography (EtOAc:MeOH, 95:5) to give the product (0.5 g, 9%).

Step C

Following a similar procedure as that used in Preparative Example 13.3 Step D, of WO 02/083624, published October 24, 2002, except using the compound from Step B above (0.14 g), the product was obtained (0.18 g, 87%, MH^+ = 256).

Step D

Following a similar procedure as that used in Preparative Example 11 Step B, of WO 02/083624, published October 24, 2002, except using the compound from Step C above (0.18 g), the product was obtained (0.17 g).

Step E

Following a similar procedure as that used in Preparative Example 13.3 Step B, of WO 02/083624, published October 24, 2002, except using the compound from Step D above (0.17 g), the product was obtained (0.17 g, 95%, MH^+ = 315).

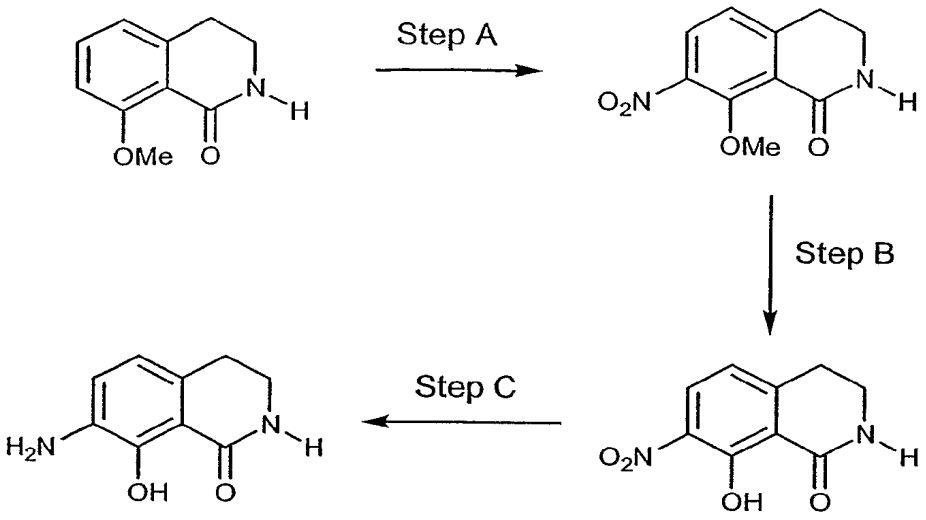
Step F

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step E above (0.17 g), the nitrophenol was obtained (0.165 g, 99%, MH^+ = 303).

Step G

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step F above (0.165 g), the title compound was obtained (0.128 g, 86%, MH^+ = 193).

PREPARATIVE EXAMPLE 1306



Step A

Following a similar procedure as that used in Preparative Example 11 Step B, of WO 02/083624, published October 24, 2002, except using the lactam (0.179 g), the title compound was obtained (0.25 g, 25%).

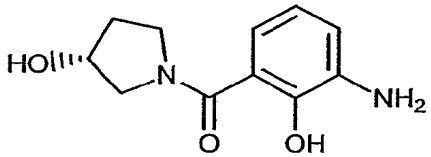
Step B

Following a similar procedure as that used in Preparative Example 13.29 Step C, except using the product from Step A above (0.055 g), the phenol was obtained (0.045 g, 99%).

Step C

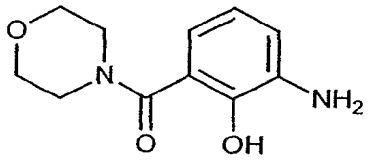
Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (0.045 g), the title compound was obtained (0.022 g, 57%, MH^+ = 179).

PREPARATIVE EXAMPLE 1307



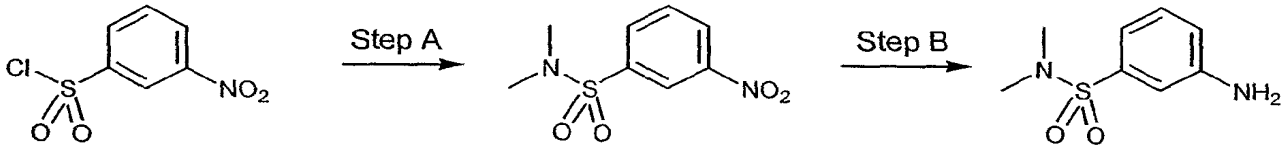
Following a similar procedure as that used in Preparative Example 2, of WO 02/083624, published October 24, 2002, except using 3(*R*)-hydroxypyrrolidine HCl (1.36 g), the title compound was obtained (2.25 g, 89%).

PREPARATIVE EXAMPLE 1308



Following a similar procedure as that used in Preparative Example 2, of WO 02/083624, published October 24, 2002, except using morpholine, the title compound was obtained (3.79 g).

PREPARATIVE EXAMPLE 1309



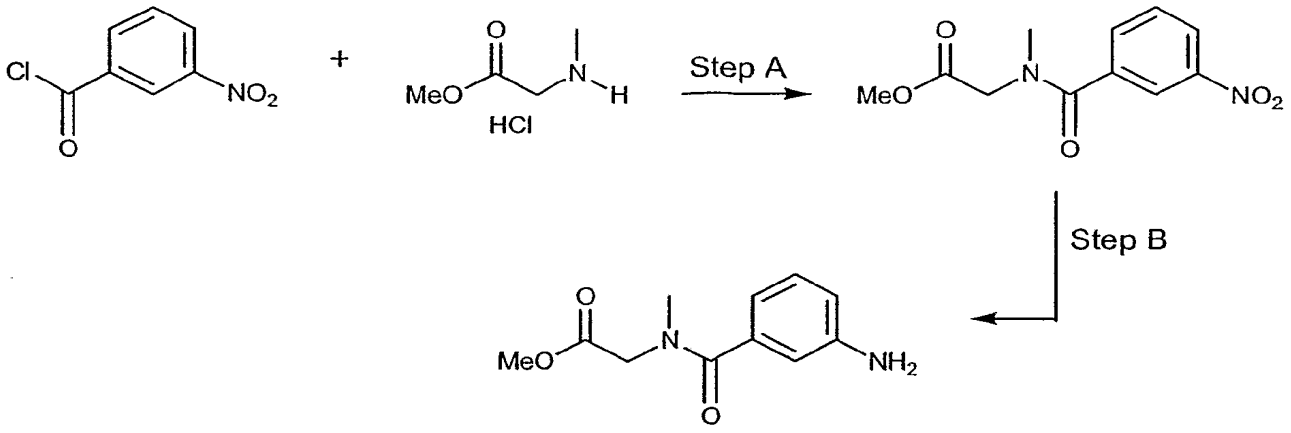
Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrophenylsulfonylchloride and diethylamine (2.2 eq), the dimethylsulfonamide was obtained (90%, MH^+ = 231).

Step B

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above, the title compound was obtained (45%, MH^+ = 201).

PREPARATIVE EXAMPLE 1310



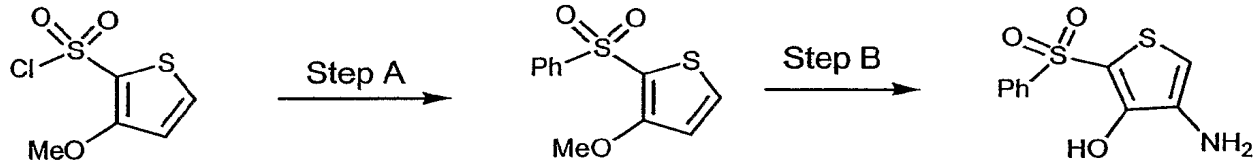
Step A

Following a similar procedure as that used in Preparative Example 13.29 Step B, except using the commercially available nitrobenzoylchloride and the commercially available amine indicated, the benzamide was obtained (13%, MH^+ = 253).

Step C

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above, the title compound was obtained (94%, MH^+ = 223).

PREPARATIVE EXAMPLE 1311



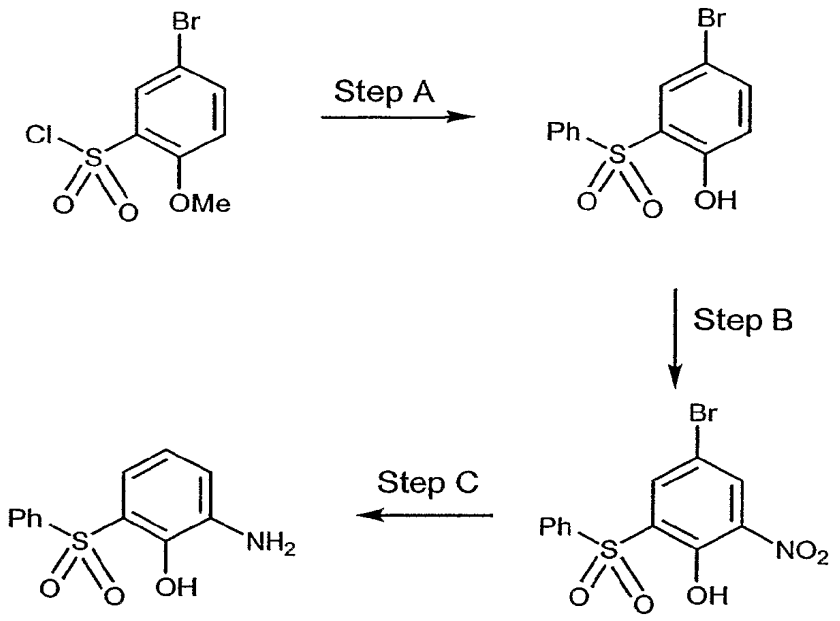
Step A

To a benzene (20 mL) solution of methoxythiophenesulfonylchloride (1.5 g) was added $AlCl_3$ (2.0 g) at RT. After 15 min, the mixture was added to 0.1N HCl (aq) with stirring, then extracted with Et_2O. Washing the organic phase with bring, drying over $MgSO_4$, concentration in vacuo and purification by silica gel chromatography (Hexane:EtOAc, 5:2) gave the title compound (1.5 g, 84%).

Step B

Following a similar procedure as that used in Preparative Example 13.29 Steps C-G, except using the product from Step A above, the title compound was obtained (3%, $MH^+ = 380$).

PREPARATIVE EXAMPLE 1312



Step A

Following a similar procedure as that used in Preparative Example 1311 Step A, except using the commercially available sulfonylchloride, the diphenylsulfone was obtained (880 mg, 80%).

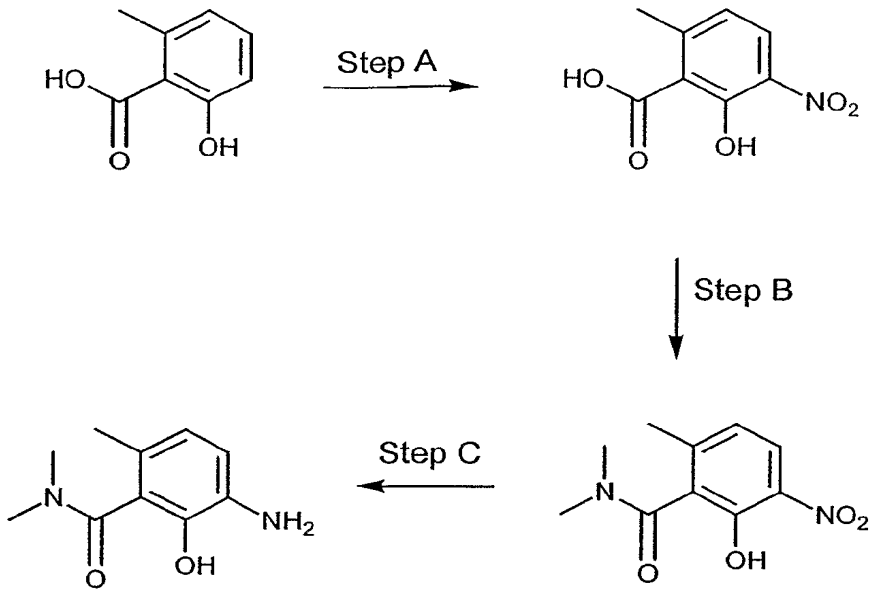
Step B

Following a similar procedure as that used in Preparative Example 11 Step B, of WO 02/083624, published October 24, 2002, except using the product from Step A above, the title compound was obtained (0.90 g, 97%).

Step C

Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (0.16 g), the title compound was obtained (0.106 g, 95%).

PREPARATIVE EXAMPLE 1313



Step A

Following a similar procedure as that used in Preparative Example 1311 Step A, except using the commercially available phenol (2 g), the nitroacid was obtained (~ 13 mmol).

Step B

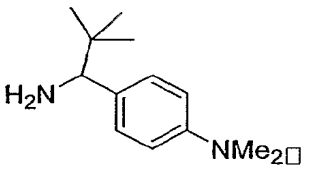
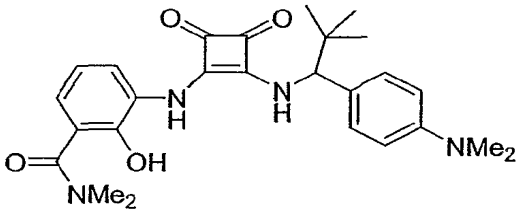
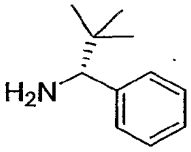
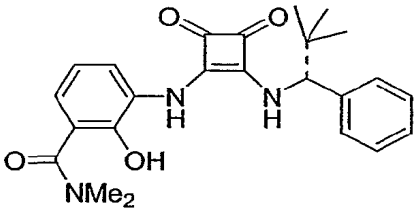
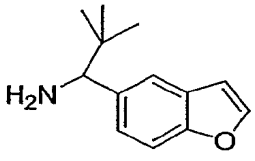
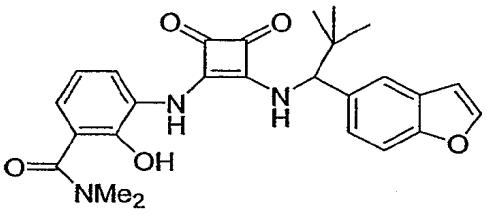
Oxallyl chloride (3.5 mL) and two drops of DMF was added to the product from Step A above (~ 13 mmol) dissolved in dichloromethane (100 mL). After stirring at RT overnight, the mixture was concentrated in vacuo, diluted with dichloromethane (50 mL), cooled to 0°C. Dimethylamine in THF (20 mL of 2N) and TEA (8 mL) were added. After 3 hr of stirring, the mixture was concentrated in vacuo, aq NaOH (1M) was added, and the mixture was extracted with dichloromethane. The pH of the aq layer was adjusted to pH = 2 using 6N HCl (aq), and extracted with dichloromethane. The combiuned organic extracts were washed with brine, dried, concentrated in vacuo, and the product purified by silica gel chromatography (700 mL dichloromethane/20 mL MeOH/ 1 mL AcOH) to give the title compound (800 mg, 27% for two steps).

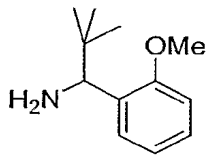
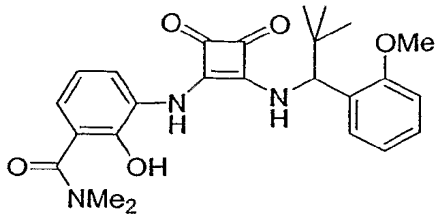
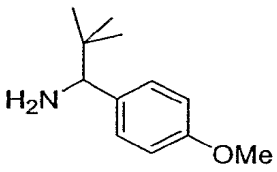
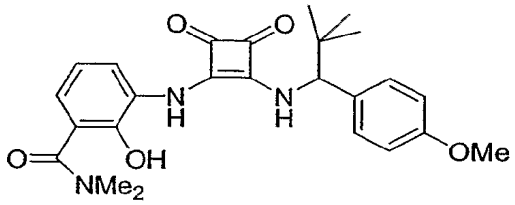
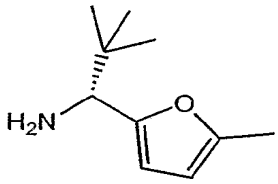
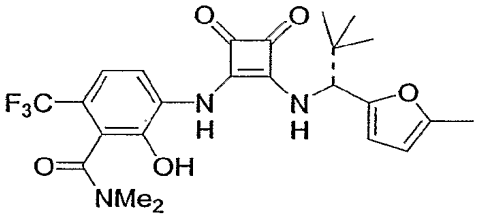
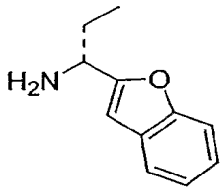
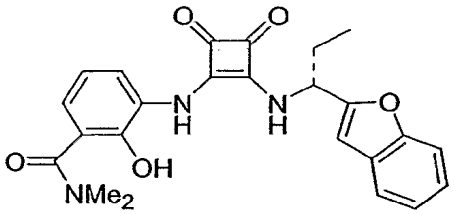
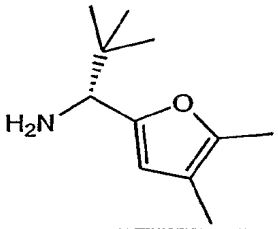
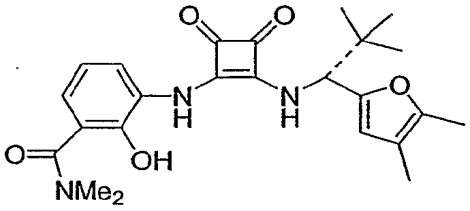
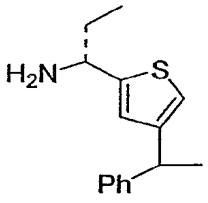
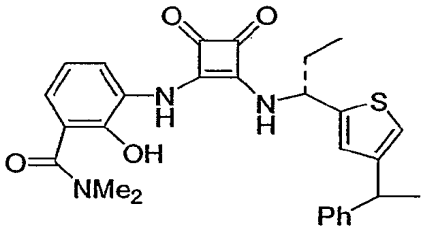
Step C

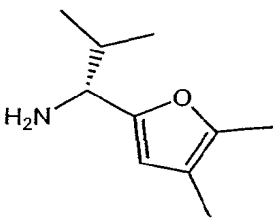
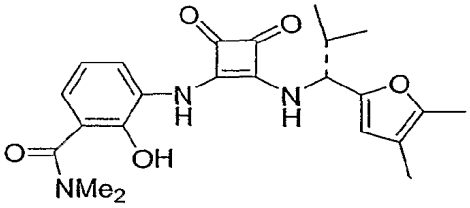
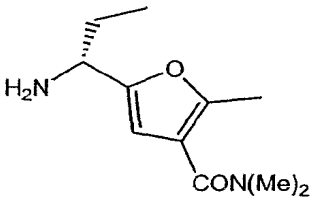
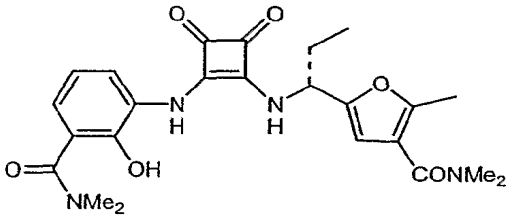
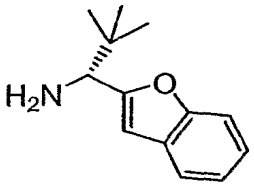
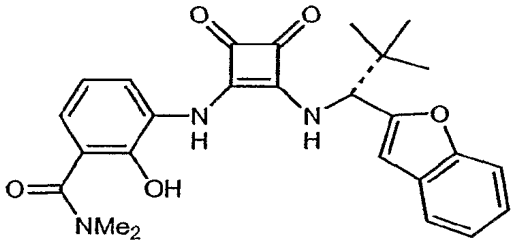
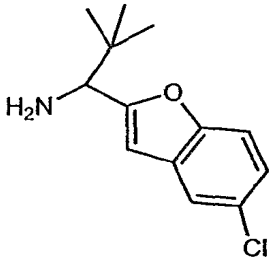
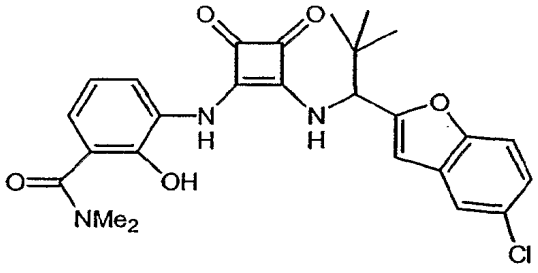
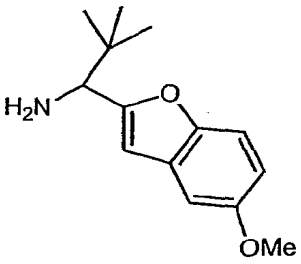
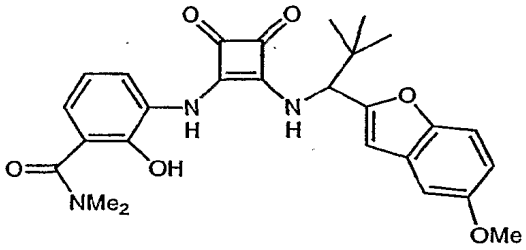
Following a similar procedure as that used in Preparative Example 10.55 Step C, of WO 02/083624, published October 24, 2002, except using the product from Step B above (780 mg), the title compound was obtained (0.46 g, 68%).

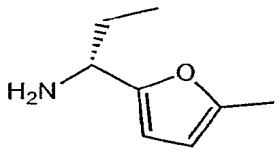
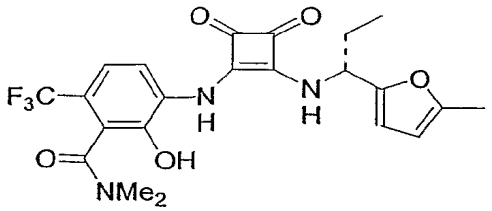
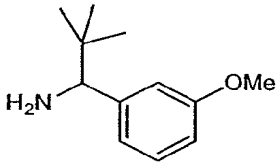
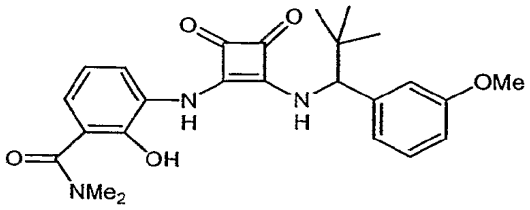
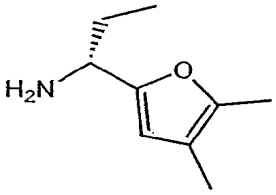
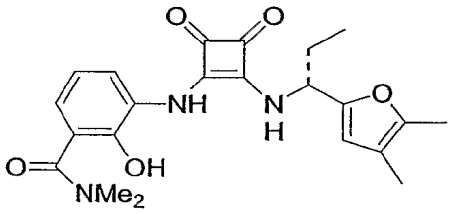
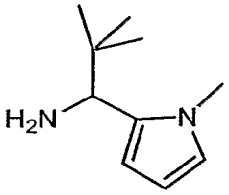
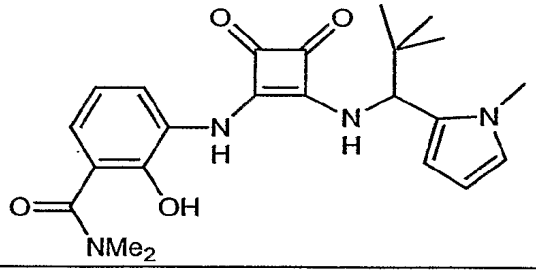
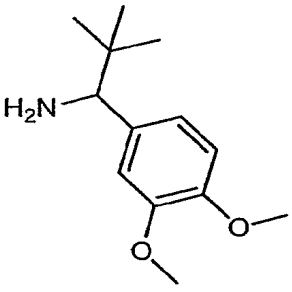
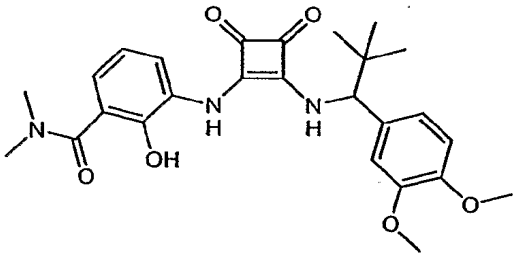
Examples 2001-2088

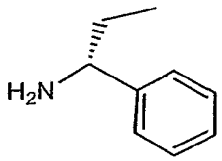
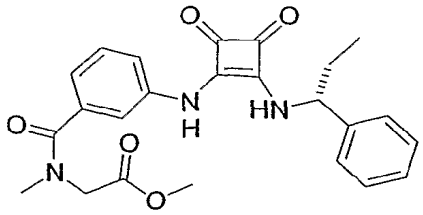
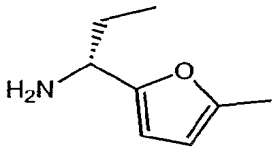
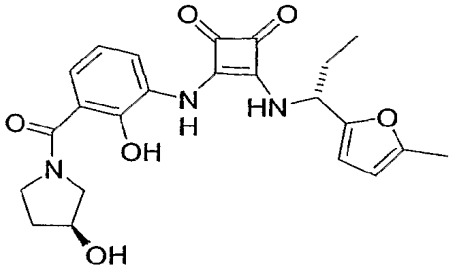
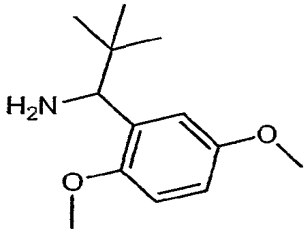
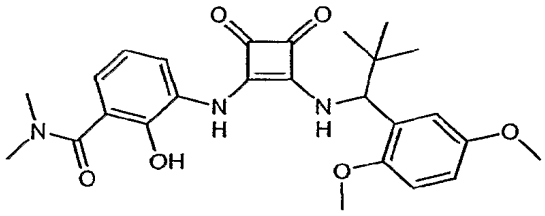
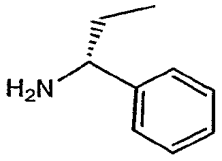
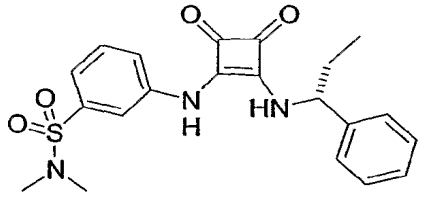
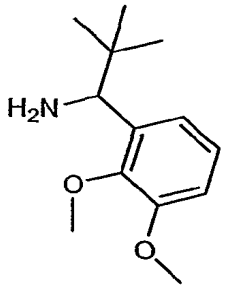
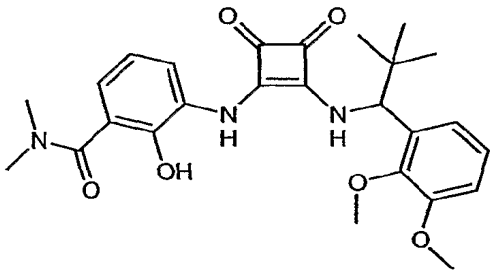
Following a similar procedure set forth in Example 210, of WO 02/083624, published October 24, 2002, but using the cyclobutenedione intermediate and amine indicated in the Table below, the following cyclobutenedione products were obtained. See WO 02/083624, published October 24, 2002, for Preparative Examples 19, 19.2, 22, 23.14 and 87.1.

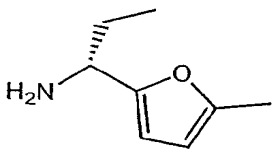
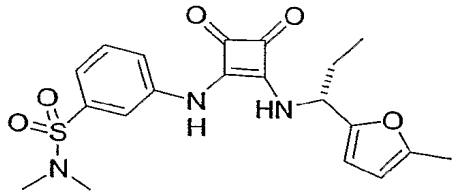
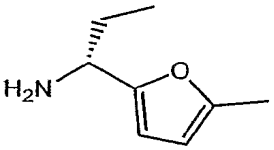
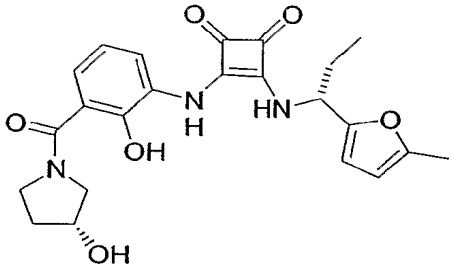
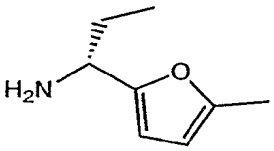
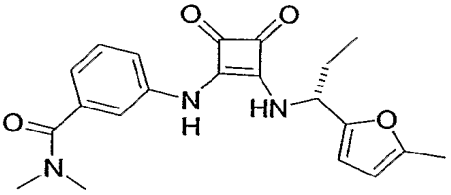
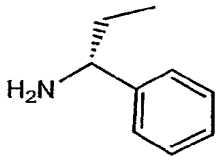
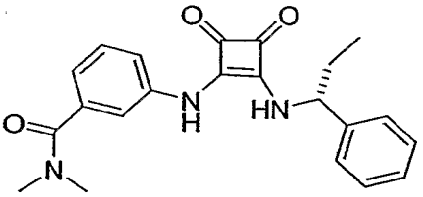
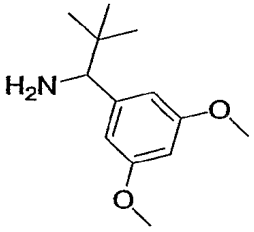
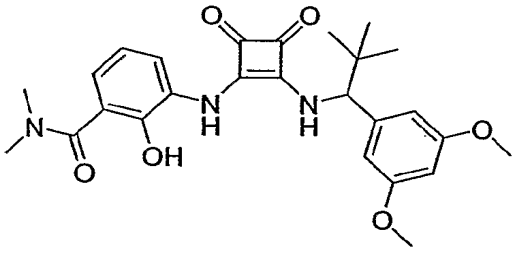
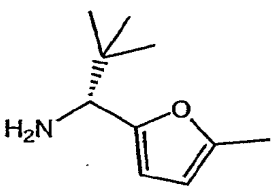
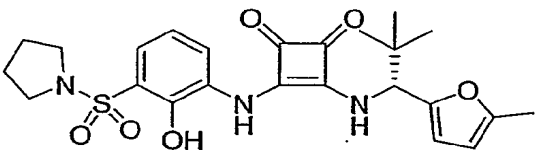
Example	Prep Ex of intermediate and Amine	Product	1.Yield (%) 2. $(M+1)^+$
2001	19 and 		3. 65% 4. 465
2002	19 and 		1. 5% 2. 422
2003	19 and 		1. 47% 2. 462

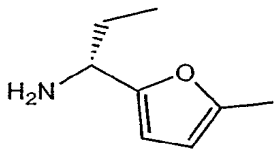
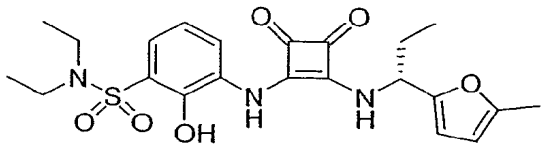
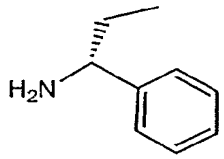
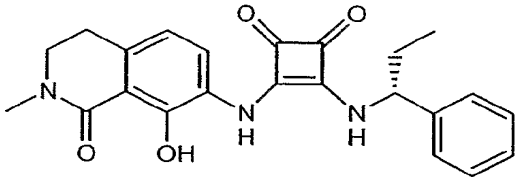
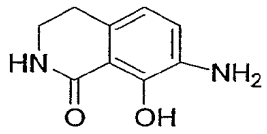
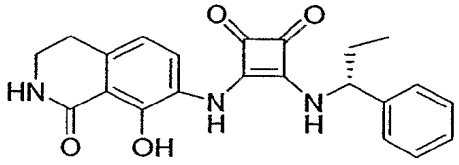
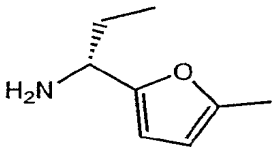
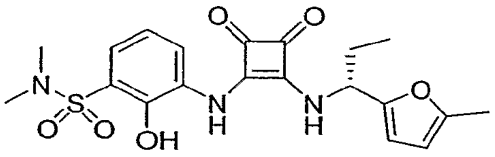
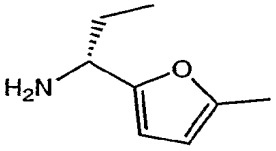
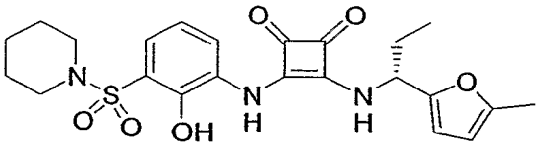
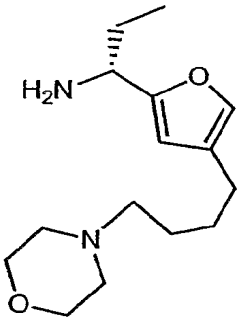
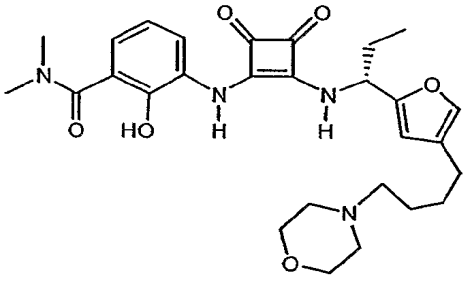
2004	19 and 		1. 74% 2. 452
2005	19 and 		1. 71% 2. 452
2006	1007 and 		1. 18% 2. 494
2007	19 and 		1. 36% 2. 434
2008	19 and 		1. 19% 2. 440
2009	19 and 		1. 45% 2. 504

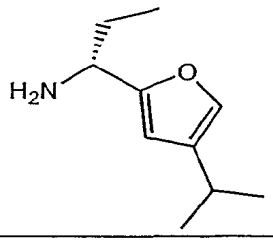
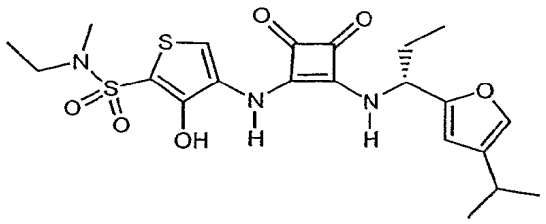
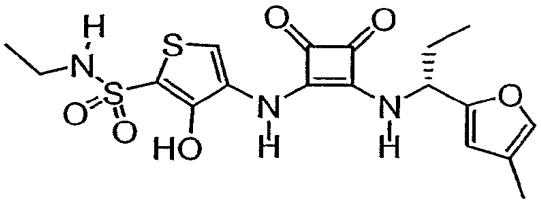
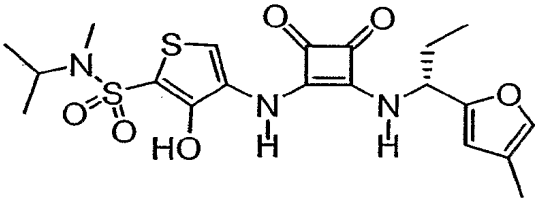
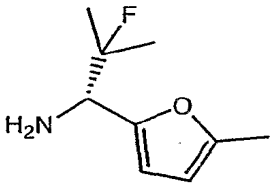
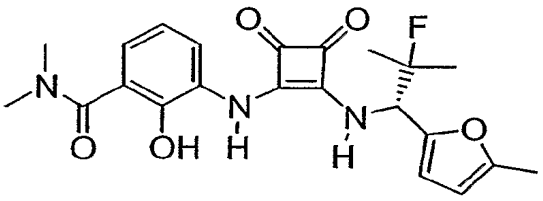
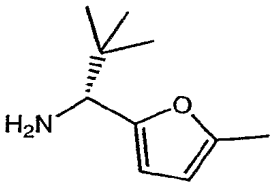
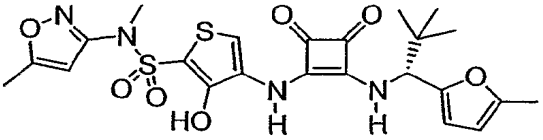
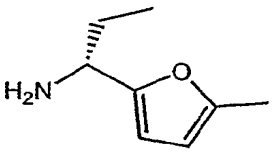
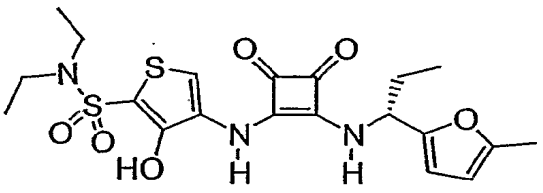
2010	19 and 		1. 57% 2. 426
2011	19 and 		1. 6% 2. 469
2012	19 and 		1. 4% 2. 462
2013	19 and 		1. 29% 2. 496
2014	19 and 		1. 17% 2. 492

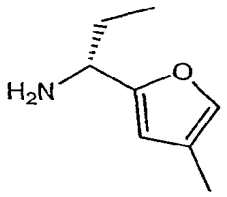
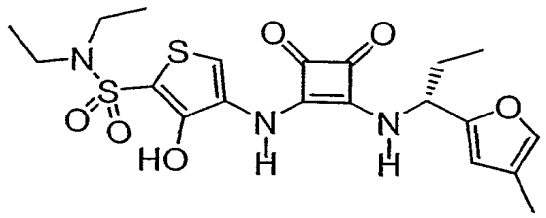
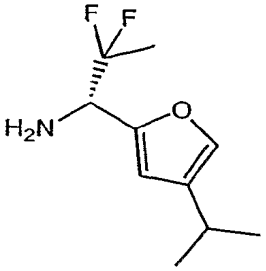
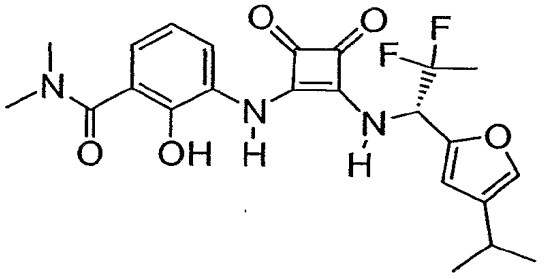
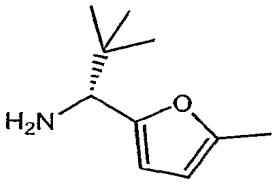
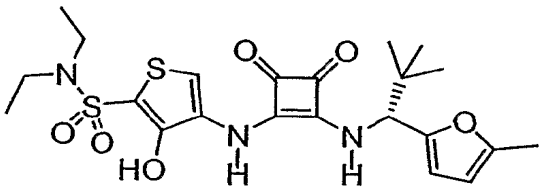
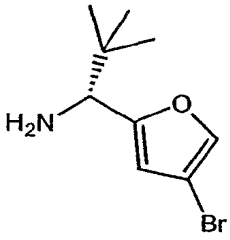
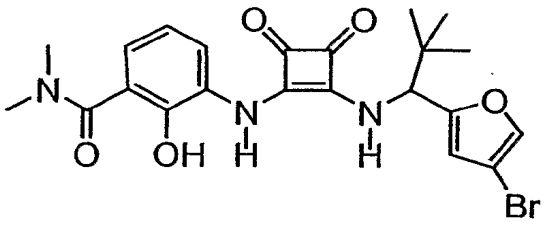
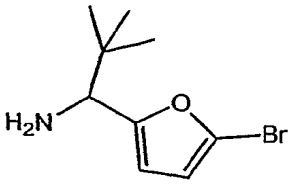
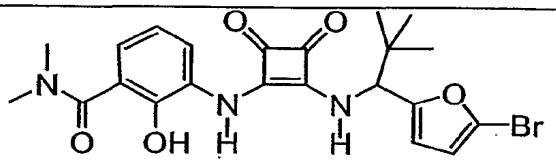
2015	1007 and 		1. 65% 2. 466
2016	19 and 		1. 72% 2. 452
2017	19 and 		1. 22% 2. 412
2018	19 and 		1. 5% 2. 425
2019	19 and 		1. 82% 2. 482

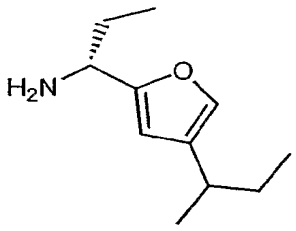
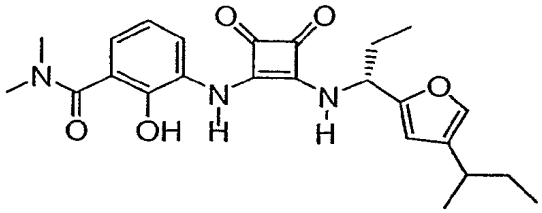
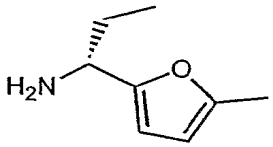
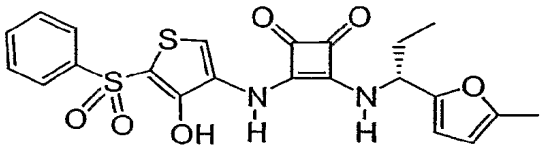
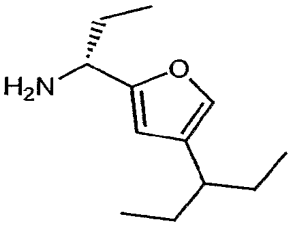
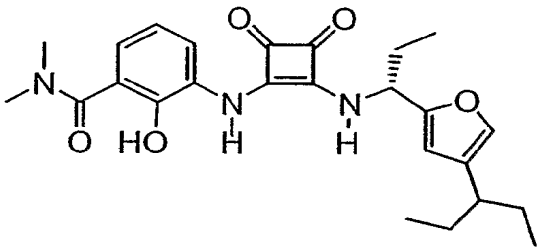
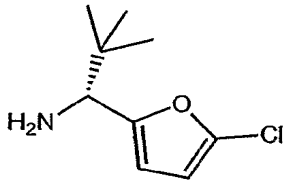
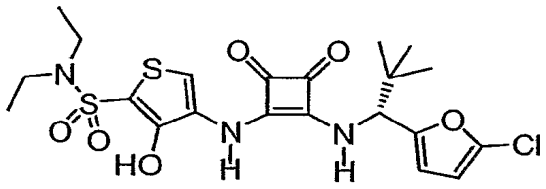
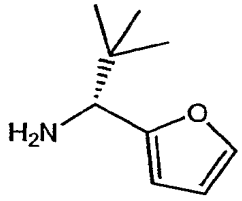
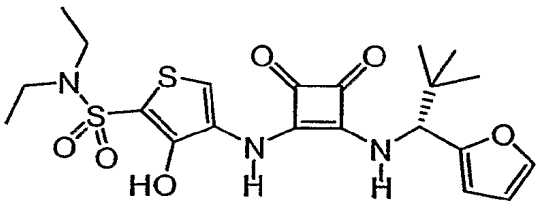
2020	1008 and 		1. 49% 2. 436
2021	22 and 		1. 45% 2. 440
2022	19 and 		1. 35% 2. 482
2024	1010 and 		1. 16% 2. 414
2026	19 and 		1. 46% 2. 482

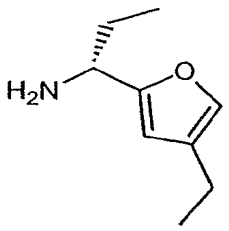
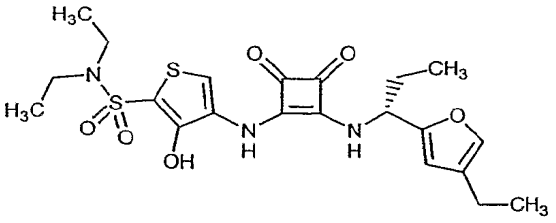
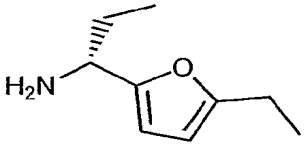
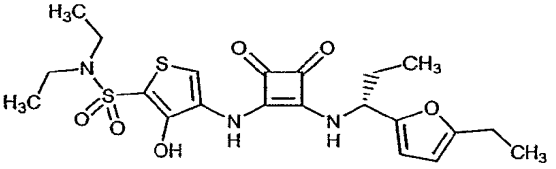
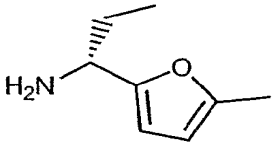
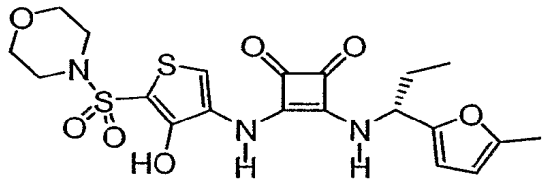
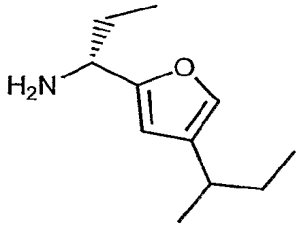
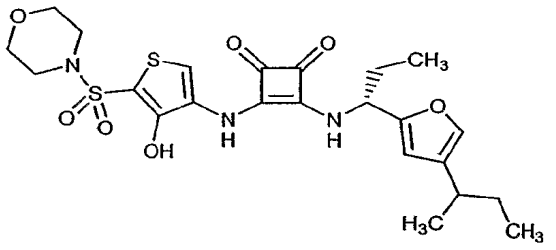
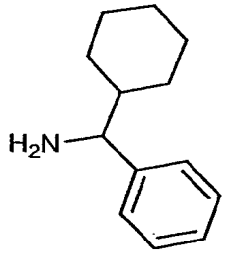
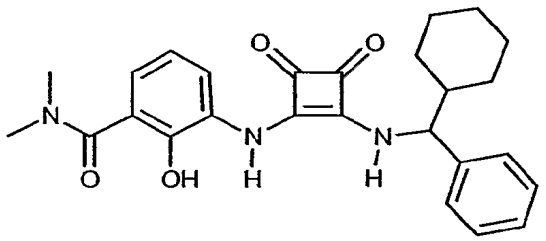
2027	1010 and 		1. 13% 2. 418
2028	1012 and 		1. 39% 2. 440
2029	19 and 		1. 55% 2. 382
2030	19 and 		1. 39% 2. 378
2033	19 and 		1. 71% 2. 482
2034	1013 and 		1. 45% 2. 487.9

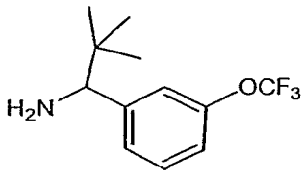
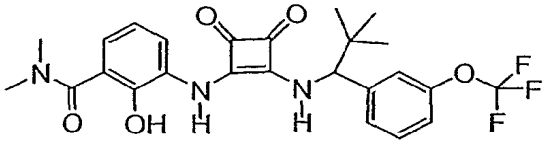
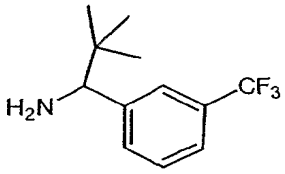
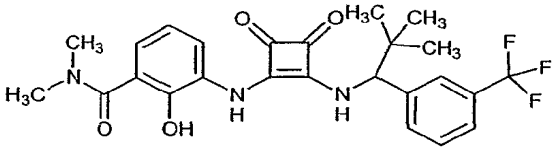
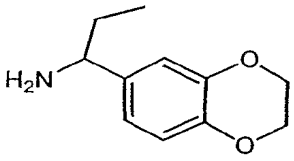
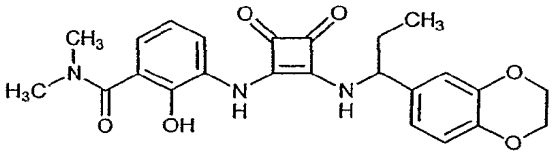
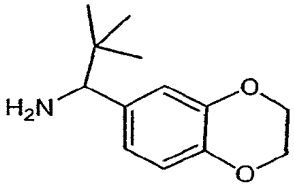
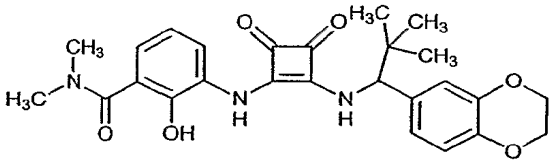
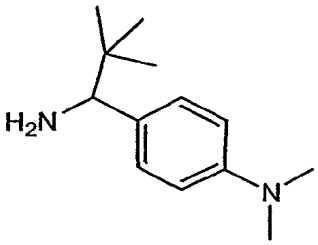
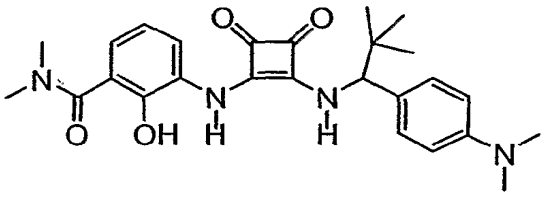
2035	1014 and 		1. 22% 2. 461.8
2036	1015 and 		1. 27% 2. 405.9
2037	87.1 and 		1. 26% 2. 392.0
2038	1016 and 		1. 28% 2. 433.8
2039	1017 and 		1. 34% 2. 473.9
2040	19 and 		1. 34% 2. 525

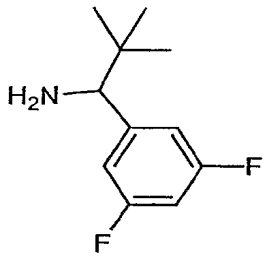
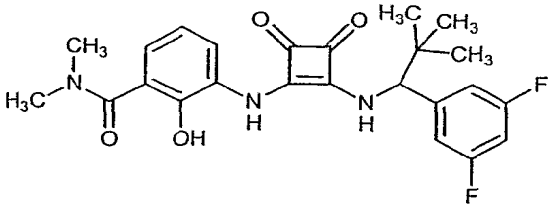
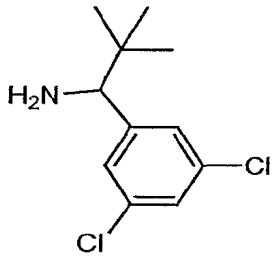
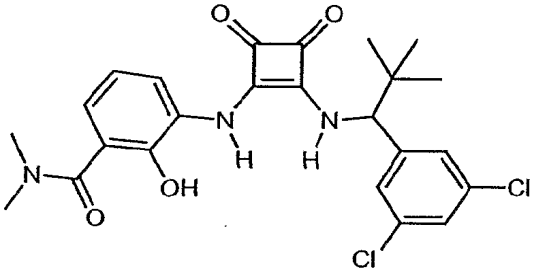
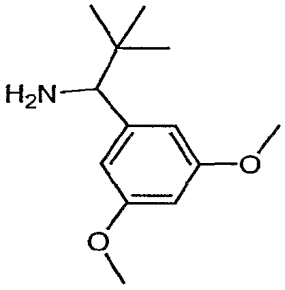
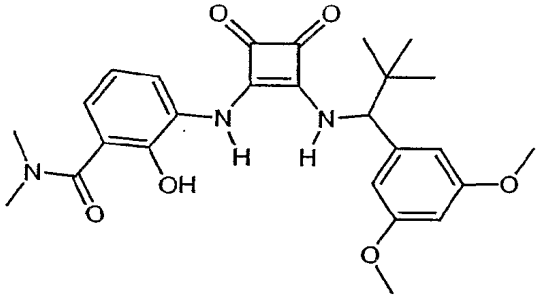
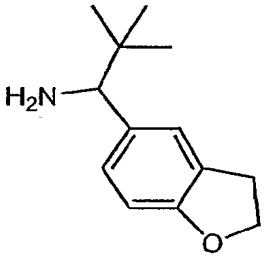
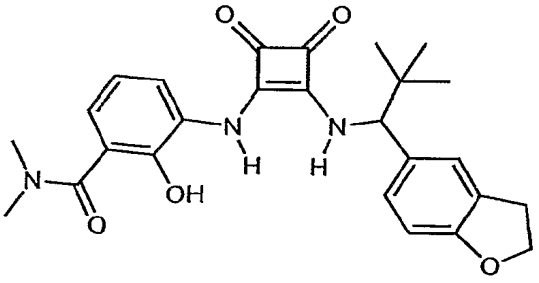
2041	23.15E and 		1. 67% 2. 482
2042	1300 and 1027		1. 33% 2. 440
2043	1203 and 1027		1. 24% 2. 468
2044	19 and 		1. 26% 2. 466
2046	19.2 and 		1. 27% 2. 535
2047	23.15F and 		1. 74% 2. 468

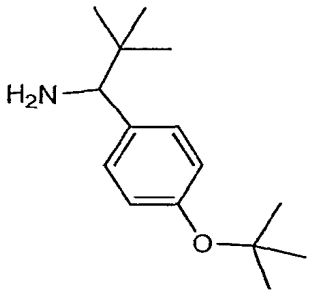
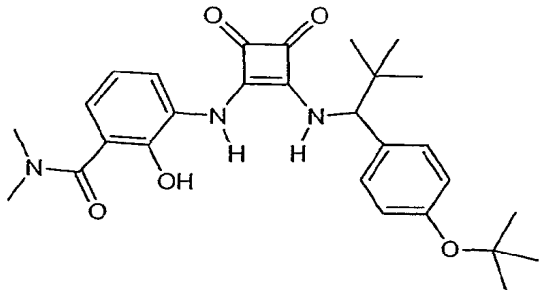
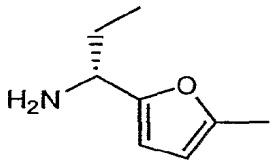
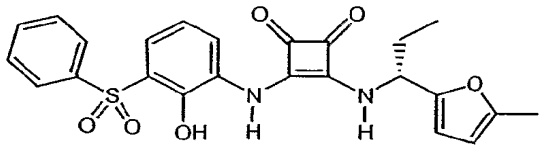
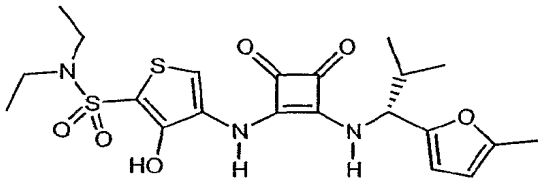
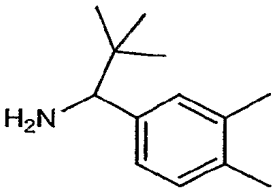
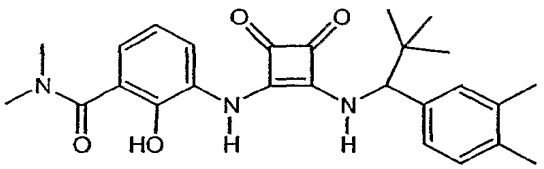
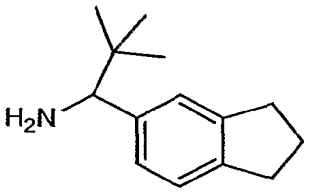
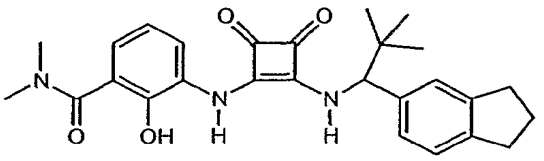
2048	23.15F and 		1. 68% 2. 468
2049	19 and 		1. 31% 2. 462
2050	23.15F and 		1. 41% 2. 496
2051	19 and 		1. 66% 2. 490
2052	19 and 		1. 43% 2. 490

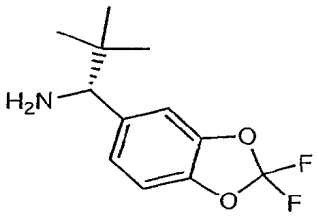
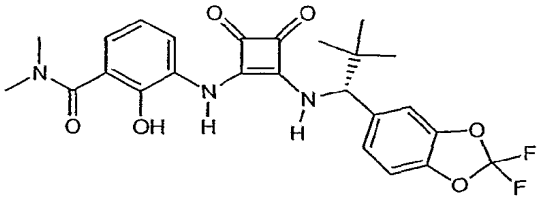
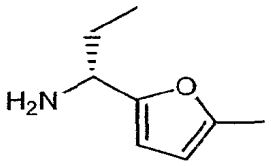
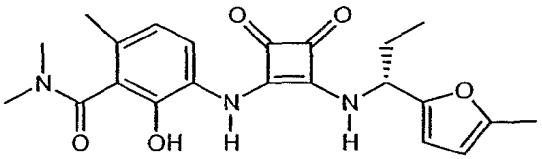
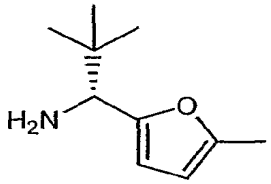
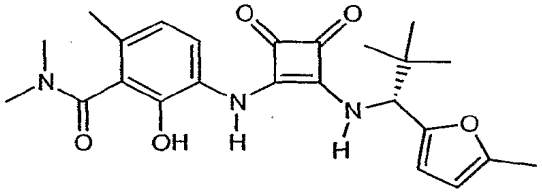
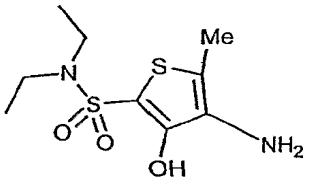
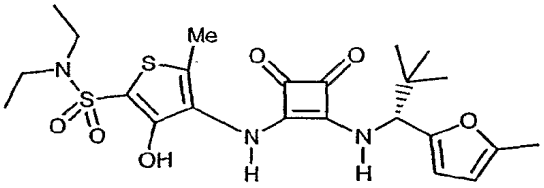
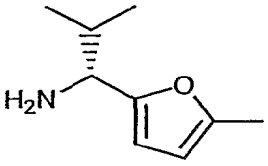
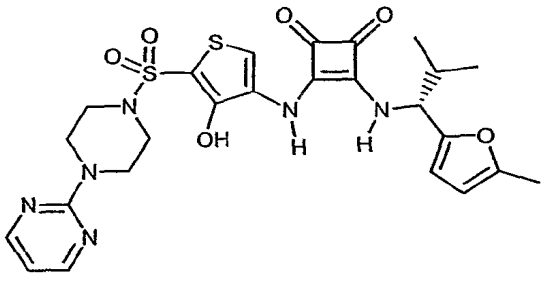
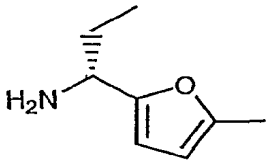
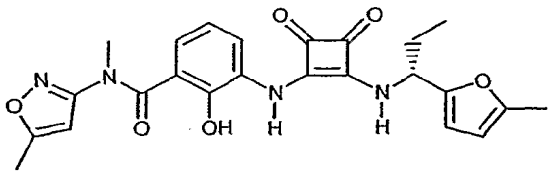
2053	19 and 		1. 76% 2. 440
2054	1024 and 		1. 15% 2. 473
2055	19 and 		1. 87% 2. 454
2056	23.15F and 		1. 52% 2. 516
2056A	23.15F and 		1. 62% 2. 482

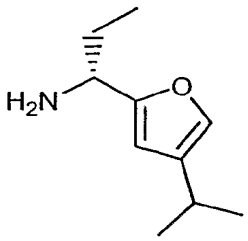
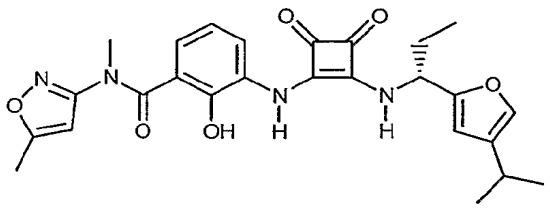
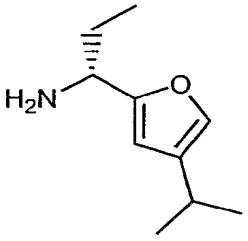
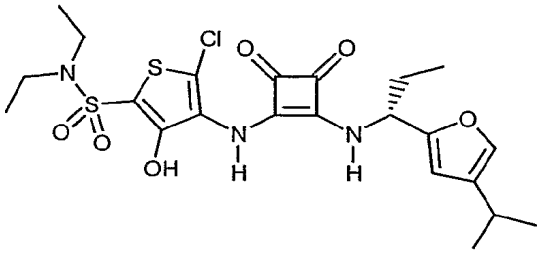
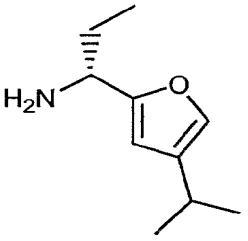
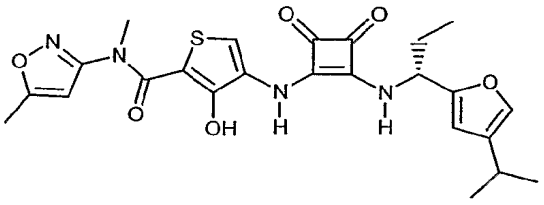
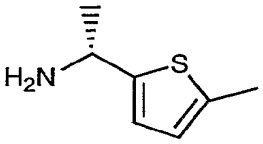
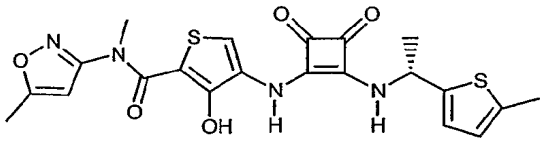
2057	23.15F and 		1. 40% 2. 482
2058	23.15F and 		1. 71% 2. 482
2059	1023 and 		1. 67% 2. 482
2060	1023 and 		1. 60% 2. 524
2061	19 and 		1. 34% 2. 448

2062	19 and 		1. 43% 2. 506
2063	19 and 		1. 53% 2. 490
2064	19 and 		1. 25% 2. 452
2065	19 and 		1. 24% 2. 480
2066	19 and 		1. 37% 2. 465

2067	19 and 		1. 38% 2. 458
2068	19 and 		1. 35% 2. 490
2069	19 and 		1. 73% 2. 482
2070	19 and 		1. 69% 2. 464

2071	19 and 		1. 71% 2. 494
2072	1022 and 		1. 54% 2. 467
2074	13.32A and 1028		1. 42% 2. 482
2075	19 and 		1. 78% 2. 450
2076	19 and 		1. 25% 2. 402

2077	19 and 		1. 33% 2. 502
2079	1021 and 		1. 23% 2. 440
2080	1021 and 		1. 15% 2. 476
2081	1029 and 		1. 17% 2. 510
2083	1020 and 		1. 46% 2. 573
2084	23.14 and 		1. 80% 2. 465

2085	23.14 and 		1. 62% 2. 493
2086	1019 and 		1. 29% 2. 530
2087	23.14 and 		1. 30% 2. 499
2088	23.14 and 		1. 13% 2. 473

Another embodiment of this invention is directed to the use of any of the compounds described above (e.g., the compounds of formulas IA, IB, 1.0A, 3.0A and the final compounds of examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof) for the manufacture of a medicament for the treatment of acute inflammation.

Another embodiment of this invention is directed to the use of any of the compounds described above (e.g., the compounds of formulas IA, IB, 1.0A, 3.0A and the final compounds of examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-

1311, and 2001-2088, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof) for the manufacture of a medicament for the treatment of acute inflammation.

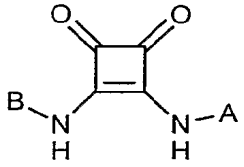
Another embodiment of this invention is directed to the use of any of the compounds described above (e.g., the compounds of formulas IA, IB, 1.0A, 3.0A and the final compounds of examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof) for the manufacture of a medicament for the treatment of rheumatoid arthritis.

Another embodiment of this invention is directed to a final compound of Examples 2006, 2010, 2015, 2029, 2034, 2035, 2038, 2039, 2047, 2050, 2074, 2079 and 2087, or a pharmaceutically acceptable salt (e.g., calcium or sodium) or solvate thereof. Other embodiments are directed to the use of these compounds for the manufacture of a medicament for the treatment of acute inflammation, or for the manufacture of a medicament for the treatment of chronic inflammation, or for the manufacture of a medicament for the treatment of rheumatoid arthritis, or for the manufacture of a medicament for the treatment of acute inflammatory pain, or for the manufacture of a medicament for the treatment of chronic inflammatory pain, or for the manufacture of a medicament for the treatment of acute neuropathic pain, or for the manufacture of a medicament for the treatment of chronic neuropathic pain, or for the manufacture of a medicament for the treatment of COPD.

While the present invention has been described in conjunction with specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:

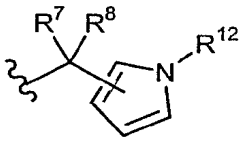


(IB)

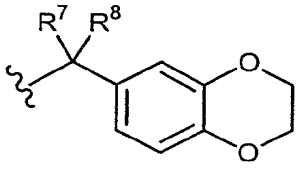
and the pharmaceutically acceptable salts and solvates thereof, wherein:

A is selected from the group consisting of:

(1)

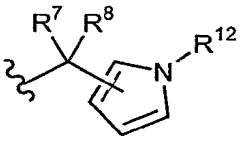


and

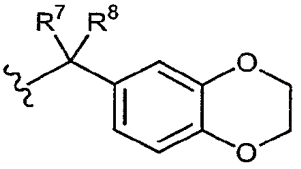


; and

(2)



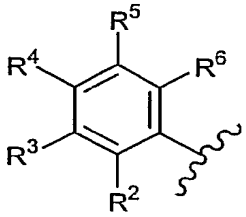
and



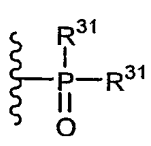
wherein said rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups; and

B is selected from the group consisting of:

(1)



provided that R^3 for this group is selected from the group consisting of: -C(O)$NR^{13}R^{14}$,



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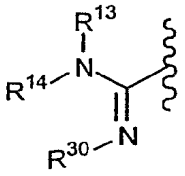
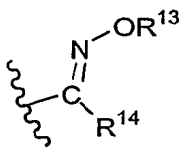


and



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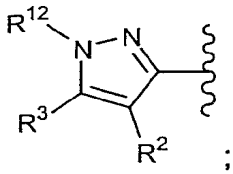
(2)



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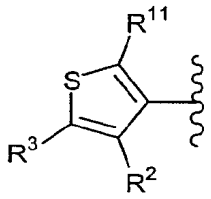
(3)



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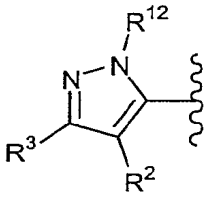
(4)



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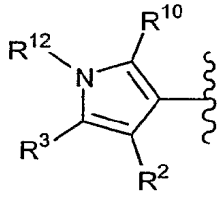
(5)



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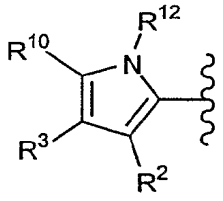
(6)



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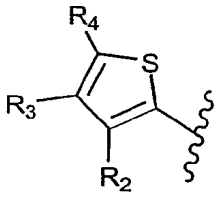
(7)



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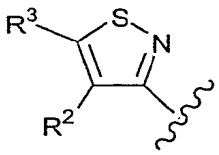
(8)



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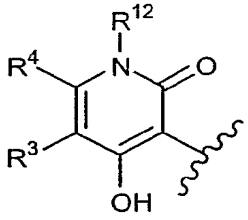

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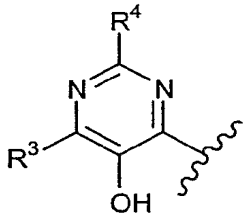

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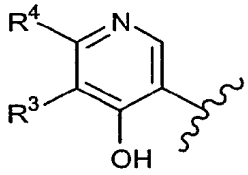
(11)



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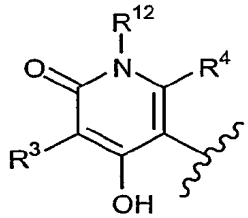

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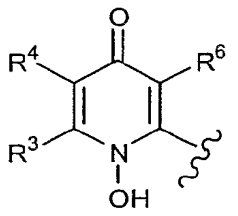
(13)



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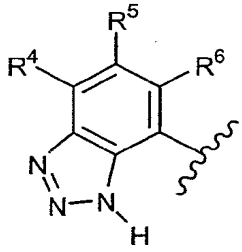
(14)



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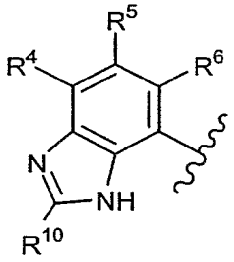
(15)



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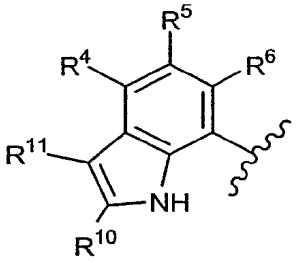

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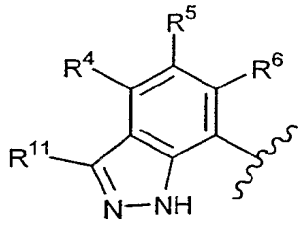
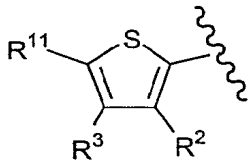
(17)



; and

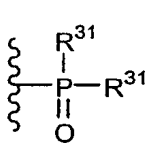
(18)



;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, - $S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,



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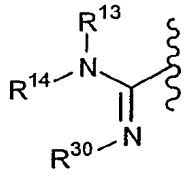
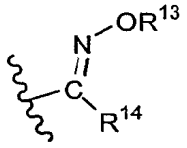


and



,

wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,
o) $-SO_2R^{13}$,
p) $-OC(O)R^{13}$,
q) $-OC(O)NR^{13}R^{14}$,
r) $-NR^{13}C(O)R^{14}$, and

s) $-NR^{13}CO_2R^{14}$;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,

b) halogen,

c) $-CF_3$,

d) $-COR^{13}$,

e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) $-CN$,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

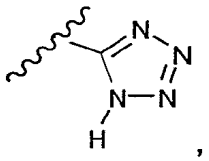
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



,

p) alkyl substituted with one or more –OH groups,

q) alkyl substituted with one or more $-NR^{13}R^{14}$ group, and

r) $-N(R^{13})SO_2R^{14}$;

each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, hydrogen, alkyl, halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$, -SH, $-SO_{(t)}NR^{13}R^{14}$, $-SO_2R^{13}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-C(O)NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, $-OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, $-C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the

substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl; wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, $-CF_3$, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, $-N(R^{40})_2$, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-S(O)_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, halogen, and $-NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups $-C(O)NR^{13}R^{14}$ and $-SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring, said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, $-C(O)OR^{15}$, $-C(O)NR^{15}R^{16}$, $-SO_tNR^{15}R^{16}$, $-C(O)R^{15}$, $-SO_2R^{15}$ provided that R^{15} is not H, $-NHC(O)NR^{15}R^{16}$, $-NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: $-SO_2$alkyl, $-SO_2$aryl, $-SO_2$cycloalkyl, and $-SO_2$heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

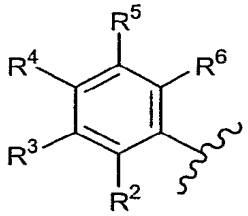
each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

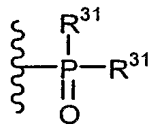
t is 0, 1 or 2.

2. The compound of Claim 1 wherein B is selected from the group consisting of:

(1)



provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,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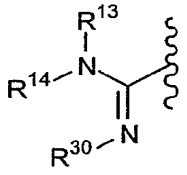
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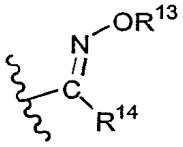
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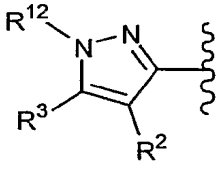
(2)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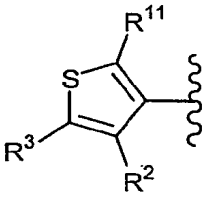
(3)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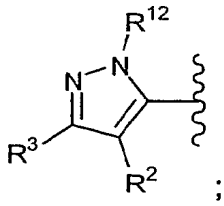
(4)



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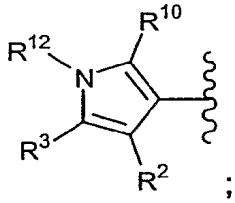
(5)



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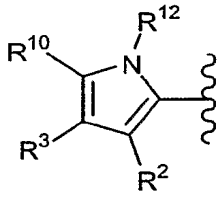
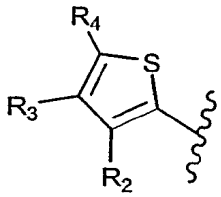
(6)



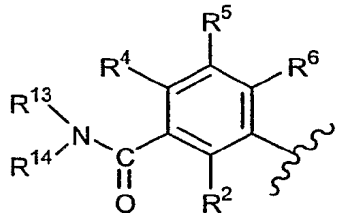
; and

(7)



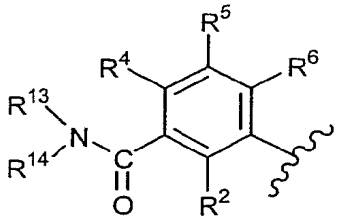
.

3. The compound of Claim 1 wherein B is:



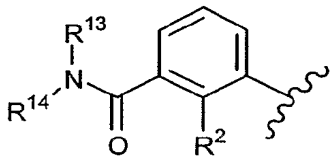
.

4. The compound of Claim 1 wherein B is:



R^2 is –OH, and R^{13} and R^{14} are each the same or different alkyl group.

5. The compound of Claim 1 wherein B is



6. The compound of Claim 5 wherein R^2 is –OH.

7. The compound of Claim 6 wherein R^{13} and R^{14} are the same or different alkyl group.

8. The compound of Claim 7 wherein R^{13} and R^{14} methyl.

9. A compound selected from the group consisting of compounds of the formulas 1.0A, 3.0A, and the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

10. The compound of Claim 9 selected from the group consisting of compounds of the formulas 1.0A and 3.0A.

11. The compound of Claim 9 selected from the group consisting of the final compounds of Examples 360.109-360.117, 368.32-368.45, 1200-1211, 1300-1311, and 2001-2088.

12. The compound of any of Claims 1 to 8 wherein said compound is a calcium or sodium salt.

13. The compound of any of Claims 9 to 11 wherein said compound is a calcium or sodium salt.

14. A pharmaceutical composition comprising an effective amount of at least one compound of any of Claims 1 to 11 and a pharmaceutically acceptable carrier.

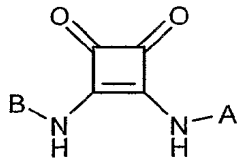
15. A pharmaceutical composition comprising an effective amount of a calcium salt or a sodium salt of at least one compound of any of Claims 1 to 11 and a pharmaceutically acceptable carrier

16. The use of at least one compound of formula IA for the manufacture of a medicament for treating a chemokine mediated disease,

said chemokine mediated disease being selected from the group consisting of: acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation, hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small

airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, chronic inflammation and rheumatoid arthritis, and

said compounds of formula IA being represented by the formula:

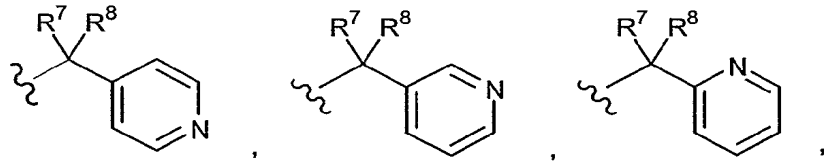


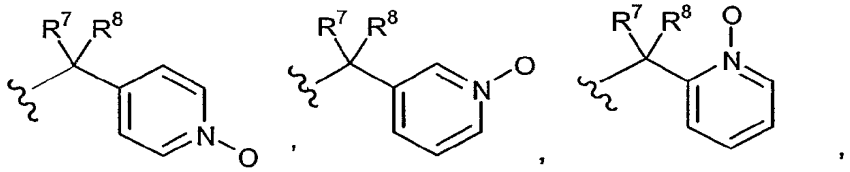
(IA)

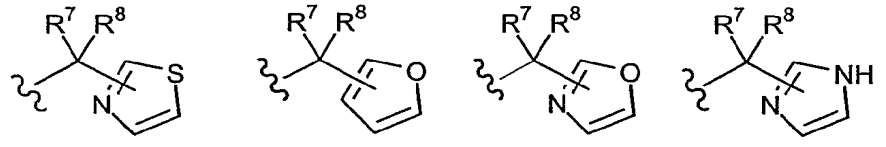
and the pharmaceutically acceptable salts and solvates thereof, wherein:

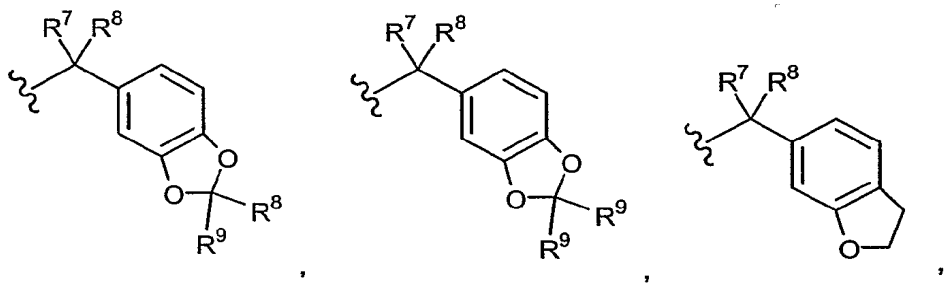
A is selected from the group consisting of:

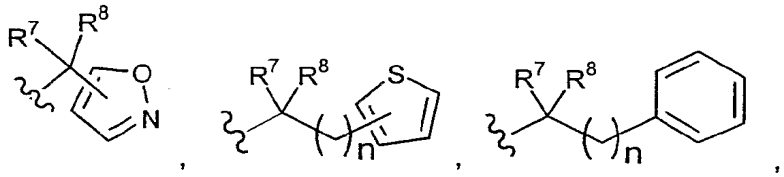
(1)

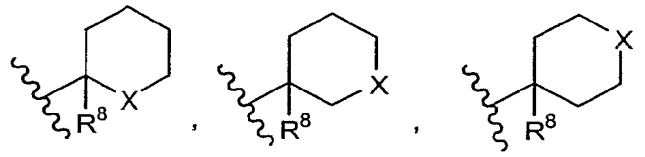


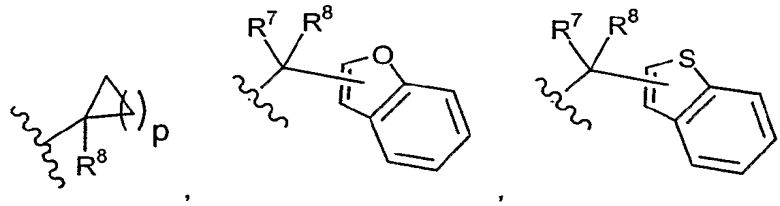


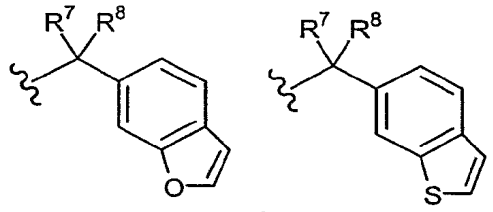


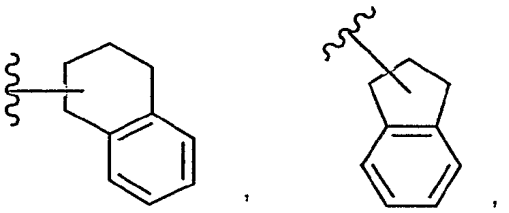


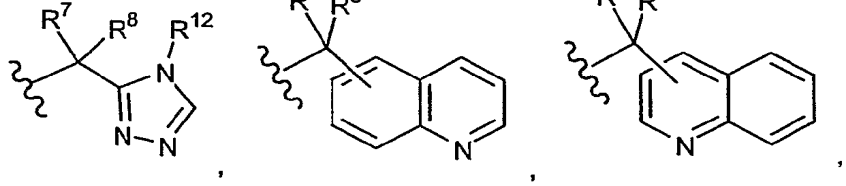


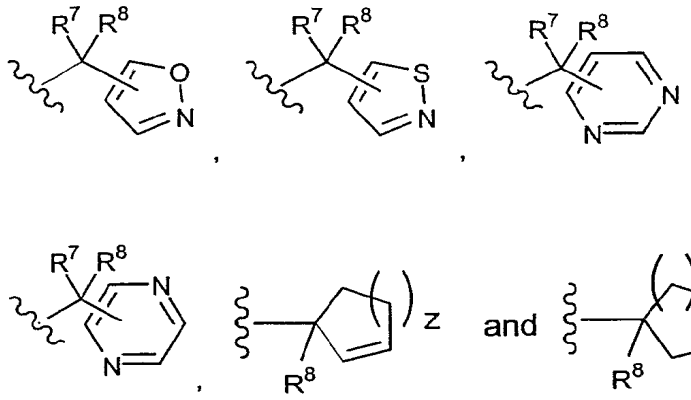




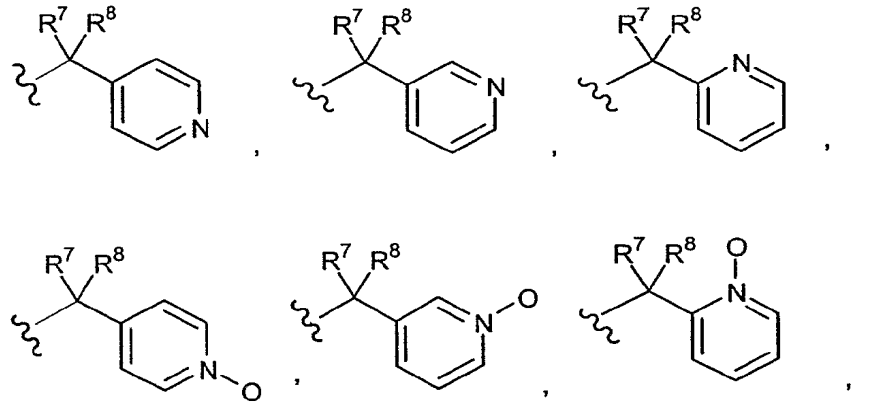


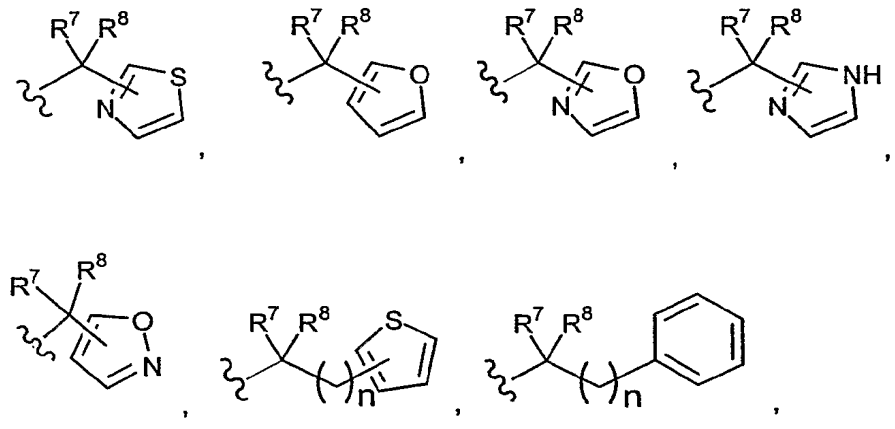


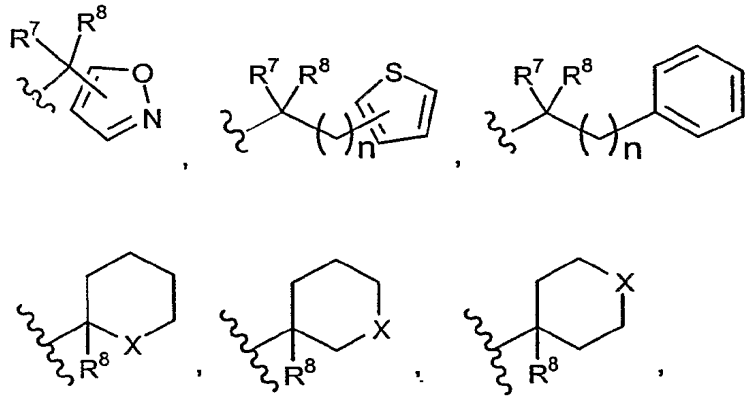


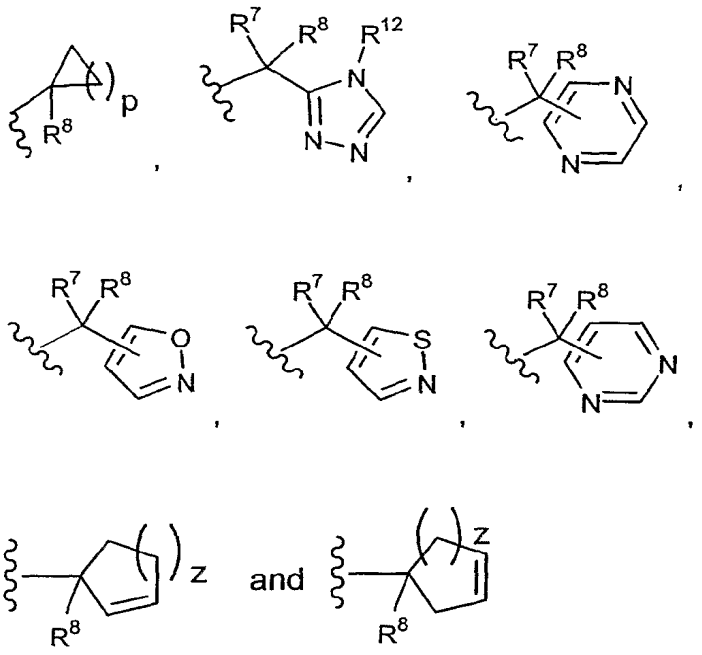


(2)



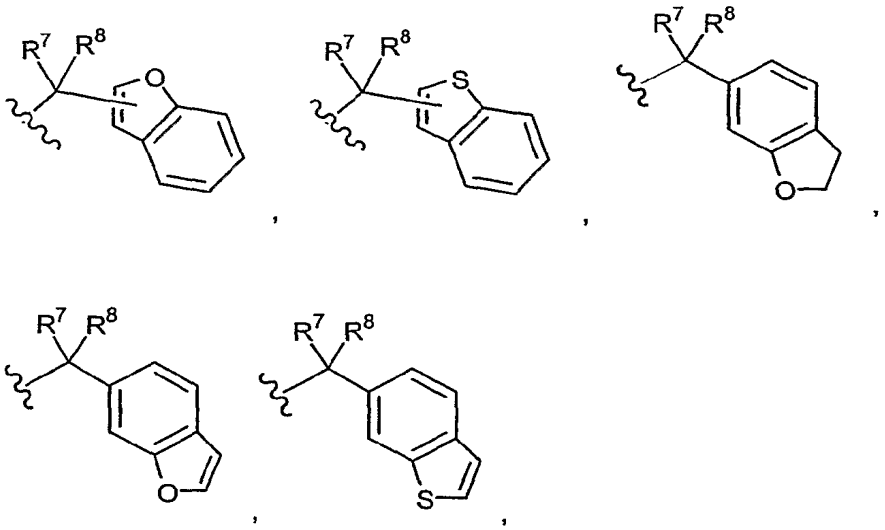


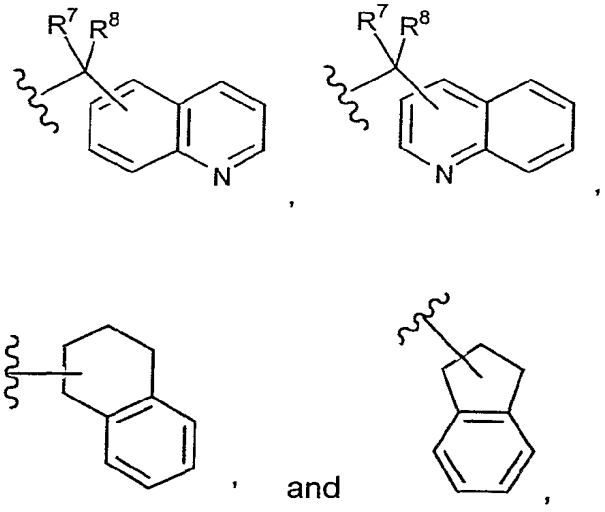




wherein the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

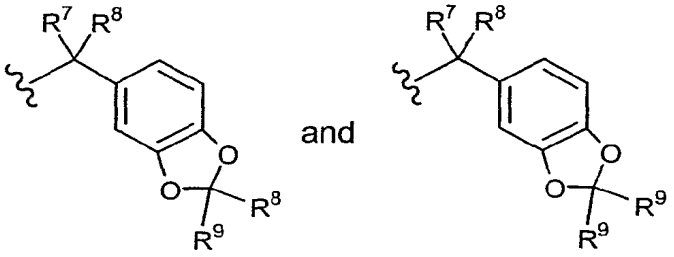
(3)





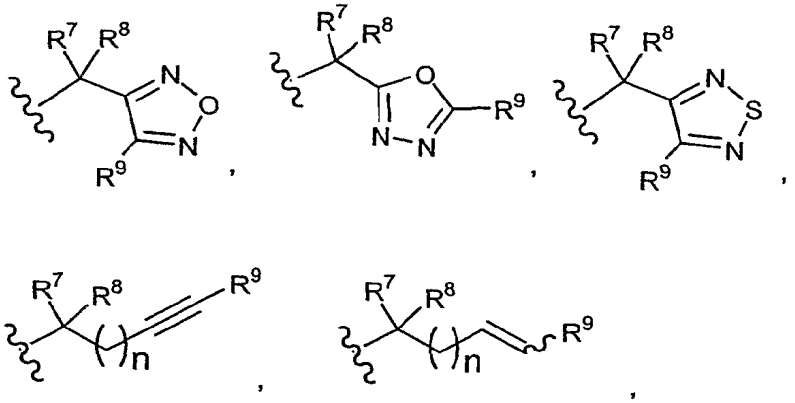
wherein one or both of the above rings of said A groups are substituted with 1 to 6 substituents each independently selected from the group consisting of: R^9 groups;

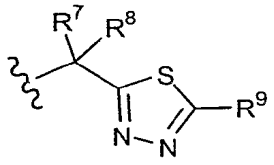
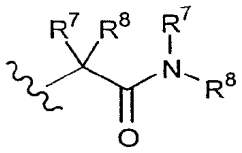
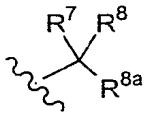
(4)



wherein the above phenyl rings of said A groups are substituted with 1 to 3 substituents each independently selected from the group consisting of: R^9 groups; and

(5)

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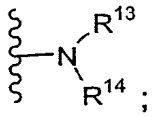
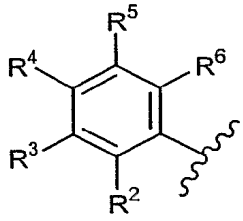

;

B is selected from the group consisting of: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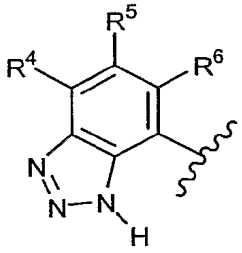
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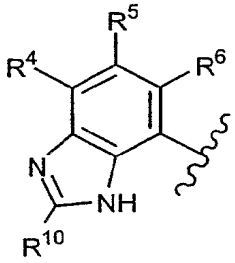
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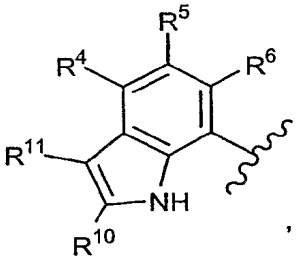
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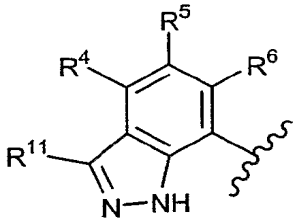
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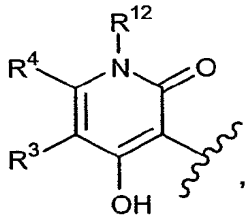
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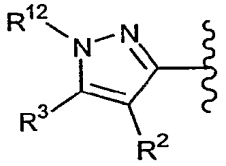
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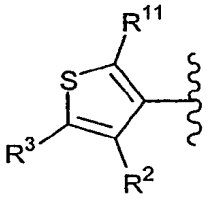
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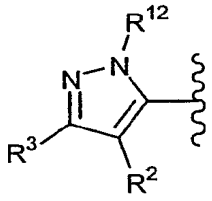
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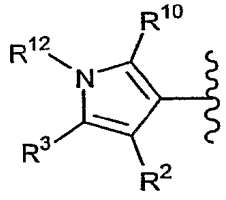
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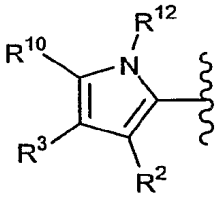
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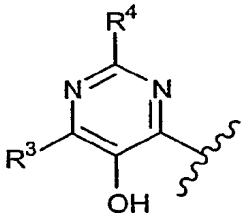
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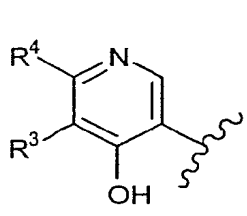
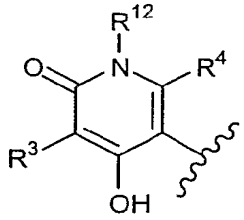
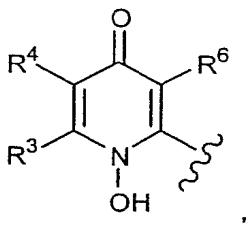
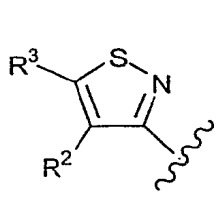
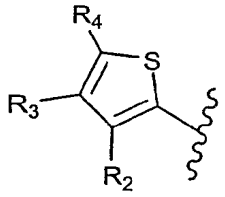
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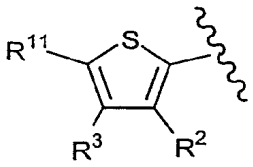

;

n is 0 to 6;

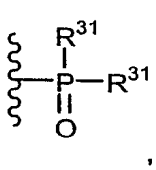
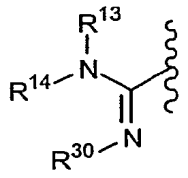
p is 1 to 5;

X is O, NH, or S;

Z is 1 to 3;

R^2 is selected from the group consisting of: hydrogen, OH, -C(O)OH, -SH, $-SO_2NR^{13}R^{14}$, $-NHC(O)R^{13}$, $-NHSO_2NR^{13}R^{14}$, $-NHSO_2R^{13}$, $-NR^{13}R^{14}$, $-C(O)NR^{13}R^{14}$, $-C(O)NHOR^{13}$, $-C(O)NR^{13}OH$, - $S(O_2)OH$, $-OC(O)R^{13}$, an unsubstituted heterocyclic acidic functional group, and a substituted heterocyclic acidic functional group; wherein there are 1 to 6 substituents on said substituted heterocyclic acidic functional group each substituent being independently selected from the group consisting of: R^9 groups;

each R^3 and R^4 is independently selected from the group consisting of: hydrogen, cyano, halogen, alkyl, alkoxy, -OH, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{17}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-SO_{(t)}R^{13}$, $-C(O)NR^{13}OR^{14}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,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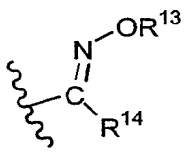
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wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^5 and R^6 are the same or different and are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, $-CF_3$, $-OCF_3$, $-NO_2$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-SO_{(t)}NR^{13}R^{14}$, $-C(O)NR^{13}OR^{14}$, cyano, unsubstituted or substituted aryl, and unsubstituted or substituted heteroaryl group; wherein there are 1 to 6 substituents on said substituted aryl group and each substituent is independently selected from the group consisting of: R^9 groups; and wherein there are 1 to 6 substituents on said substituted heteroaryl group and each substituent is independently selected from the group consisting of: R^9 groups;

each R^7 and R^8 is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, alkynyl, alkenyl, and cycloalkenyl; and wherein there are one or more substituents on said substituted R^7 and R^8 groups, wherein each substitutent is independently selected from the group consisting of:

a) halogen,
b) $-CF_3$,
c) $-COR^{13}$,
d) $-OR^{13}$,
e) $-NR^{13}R^{14}$,
f) $-NO_2$,
g) $-CN$,
h) $-SO_2OR^{13}$,
i) $-Si(alkyl)_3$, wherein each alkyl is independently selected,
j) $-Si(aryl)_3$, wherein each alkyl is independently selected,
k) $-(R^{13})_2R^{14}Si$, wherein each R^{13} is independently selected,
l) $-CO_2R^{13}$,
m) $-C(O)NR^{13}R^{14}$,
n) $-SO_2NR^{13}R^{14}$,

o) $-SO_2R^{13}$,

p) $-OC(O)R^{13}$,

q) $-OC(O)NR^{13}R^{14}$,

r) $-NR^{13}C(O)R^{14}$, and

s) $-NR^{13}CO_2R^{14}$;

R^{8a} is selected from the group consisting of: hydrogen, alkyl, cycloalkyl and cycloalkylalkyl;

each R^9 is independently selected from the group consisting of:

a) $-R^{13}$,

b) halogen,

c) $-CF_3$,

d) $-COR^{13}$,

e) $-OR^{13}$,

f) $-NR^{13}R^{14}$,

g) $-NO_2$,

h) –CN,

i) $-SO_2R^{13}$,

j) $-SO_2NR^{13}R^{14}$,

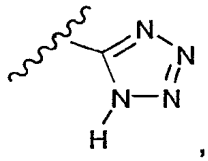
k) $-NR^{13}COR^{14}$,

l) $-CONR^{13}R^{14}$,

m) $-NR^{13}CO_2R^{14}$,

n) $-CO_2R^{13}$,

o)



,

p) alkyl substituted with one or more –OH groups,

q) alkyl substituted with one or more $-NR^{13}R^{14}$ group, and

r) $-N(R^{13})SO_2R^{14}$;

each R^{10} and R^{11} is independently selected from the group consisting of R^{13}, hydrogen, alkyl, halogen, $-CF_3$, $-OCF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, -OH, $-C(O)OR^{13}$,

-SH, -$SO_{(t)}NR^{13}R^{14}$, -SO_2R^{13}, -$NHC(O)R^{13}$, -$NHSO_2NR^{13}R^{14}$, -$NHSO_2R^{13}$, -$C(O)NR^{13}R^{14}$, -$C(O)NR^{13}OR^{14}$, -$OC(O)R^{13}$ and cyano;

R^{12} is selected from the group consisting of: hydrogen, -$C(O)OR^{13}$, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkylalkyl, and unsubstituted or substituted heteroarylalkyl group; wherein there are 1 to 6 substituents on the substituted R^{12} groups and each substituent is independently selected from the group consisting of: R^9 groups;

each R^{13} and R^{14} is independently selected from the group consisting of: H, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted arylalkyl, unsubstituted or substituted heteroarylalkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkylalkyl, unsubstituted or substituted heterocyclic, unsubstituted or substituted fluoroalkyl, and unsubstituted or substituted heterocycloalkylalkyl; wherein there are 1 to 6 substituents on said substituted R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, -CF_3, -OH, alkoxy, aryl, arylalkyl, fluroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, -$N(R^{40})_2$, -$C(O)OR^{15}$, -$C(O)NR^{15}R^{16}$, -$S(O)_tNR^{15}R^{16}$, -$C(O)R^{15}$, -SO_2R^{15} provided that R^{15} is not H, halogen, and -$NHC(O)NR^{15}R^{16}$; or

R^{13} and R^{14} taken together with the nitrogen they are attached to in the groups -$C(O)NR^{13}R^{14}$ and -$SO_2NR^{13}R^{14}$ form an unsubstituted or substituted saturated heterocyclic ring, said ring optionally containing one additional heteroatom selected from the group consisting of: O, S and NR^{18}; wherein there are 1 to 3 substituents on the substituted cyclized R^{13} and R^{14} groups and each substituent is independently selected from the group consisting of: alkyl, aryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, arylalkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, amino, -$C(O)OR^{15}$, -$C(O)NR^{15}R^{16}$, -$SO_tNR^{15}R^{16}$, -$C(O)R^{15}$, -SO_2R^{15} provided that R^{15} is not H, -$NHC(O)NR^{15}R^{16}$, -$NHC(O)OR^{15}$, halogen, and a heterocycloalkenyl group,

each R^{15} and R^{16} is independently selected from the group consisting of: H, alkyl, aryl, arylalkyl, cycloalkyl and heteroaryl;

R^{17} is selected from the group consisting of: -SO_2alkyl, -SO_2aryl, -SO_2cycloalkyl, and -SO_2heteroaryl;

R^{18} is selected from the group consisting of: H, alkyl, aryl, heteroaryl, $-C(O)R^{19}$, $-SO_2R^{19}$ and $-C(O)NR^{19}R^{20}$;

each R^{19} and R^{20} is independently selected from the group consisting of: alkyl, aryl and heteroaryl;

R^{30} is selected from the group consisting of: alkyl, cycloalkyl, -CN, $-NO_2$, or $-SO_2R^{15}$ provided that R^{15} is not H;

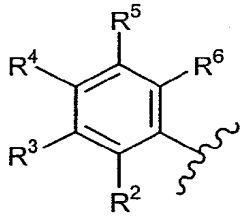
each R^{31} is independently selected from the group consisting of: unsubstituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted cycloalkyl; wherein there are 1 to 6 substituents on said substituted R^{31} groups and each substituent is independently selected from the group consisting of: alkyl, halogen and $-CF_3$;

each R^{40} is independently selected from the group consisting of: H, alkyl and cycloalkyl; and

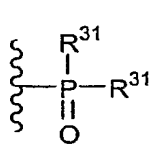
t is 0, 1 or 2.

17. The use of Claim 16 wherein B is selected from the group consisting of:

(1)



provided that R^3 for this group is selected from the group consisting of: $-C(O)NR^{13}R^{14}$,



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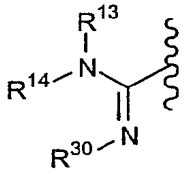
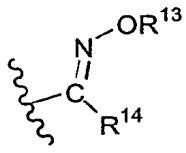


and



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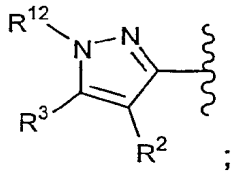
(2)



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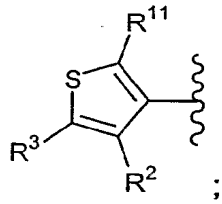
(3)



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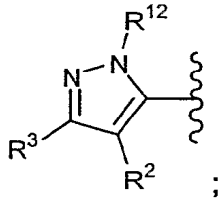
(4)



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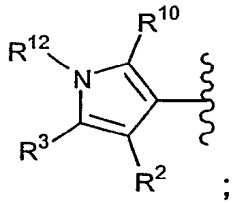
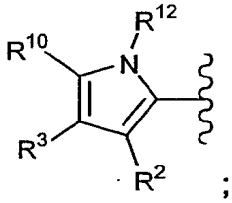
(5)



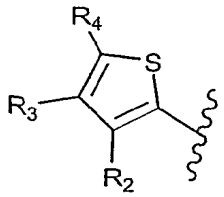
;

(6)

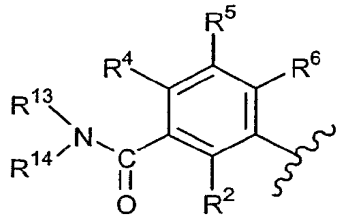


; and

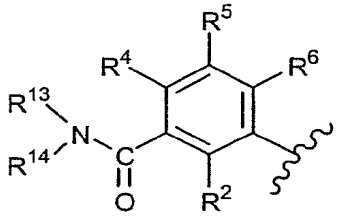
(7)



18. The use of Claim 16 wherein B is:

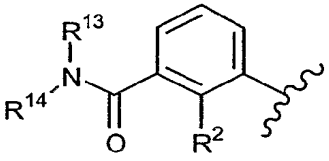


19. The use of Claim 16 wherein B is:



R^2 is –OH, and R^{13} and R^{14} are each the same or different alkyl group.

20. The use of Claim 16 wherein B is

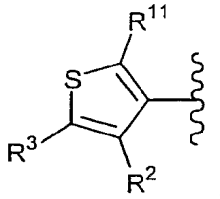


21. The use of Claim 20 wherein R^2 is –OH.

22. The use of Claim 21 wherein R^{13} and R^{14} are the same or different alkyl group.

23. The use of Claim 22 wherein R^{13} and R^{14} methyl.

24. The use of Claim 16 wherein B is



25. The use of Claim 24 wherein R^{11} is H.

26. The use of Claim 25 wherein R^2 is –OH.

27. The use of Claim 26 wherein R^3 is $-C(O)NR^{13}R^{14}$.

28. The use of Claim 27 wherein R^{13} and R^{14} are each independently selected from the group consisting of: alkyl, unsubstituted heteroaryl and substituted heteroaryl.

29. The use of Claim 24 wherein R^3 is $-S(O)_tNR^{13}R^{14}$.

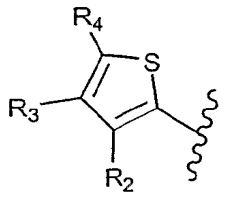
30. The use of Claim 29 wherein R^2 is –OH.

31. The use of Claim 30 wherein the R^{13} and R^{14} substituents are the same or different and are selected from the group consisting of: H and alkyl.

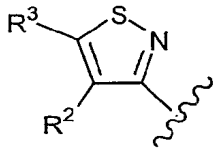
32. The use of Claim 31 wherein each R^{13} and R^{14} are independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl.

33. The use of Claim 32 wherein R^{13} and R^{14} are ethyl.

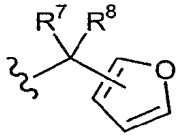
34. The use of Claim 16 wherein B is



35. The use of Claim 16 wherein B is

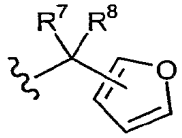


36. The use of any of Claims 16 to 35 wherein A is



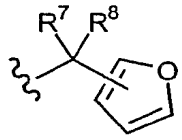
wherein the furan ring is unsubstituted or substituted.

37. The use of Claim 36 wherein A is



wherein the furan ring is substituted.

38. The use of Claim 37 wherein A is



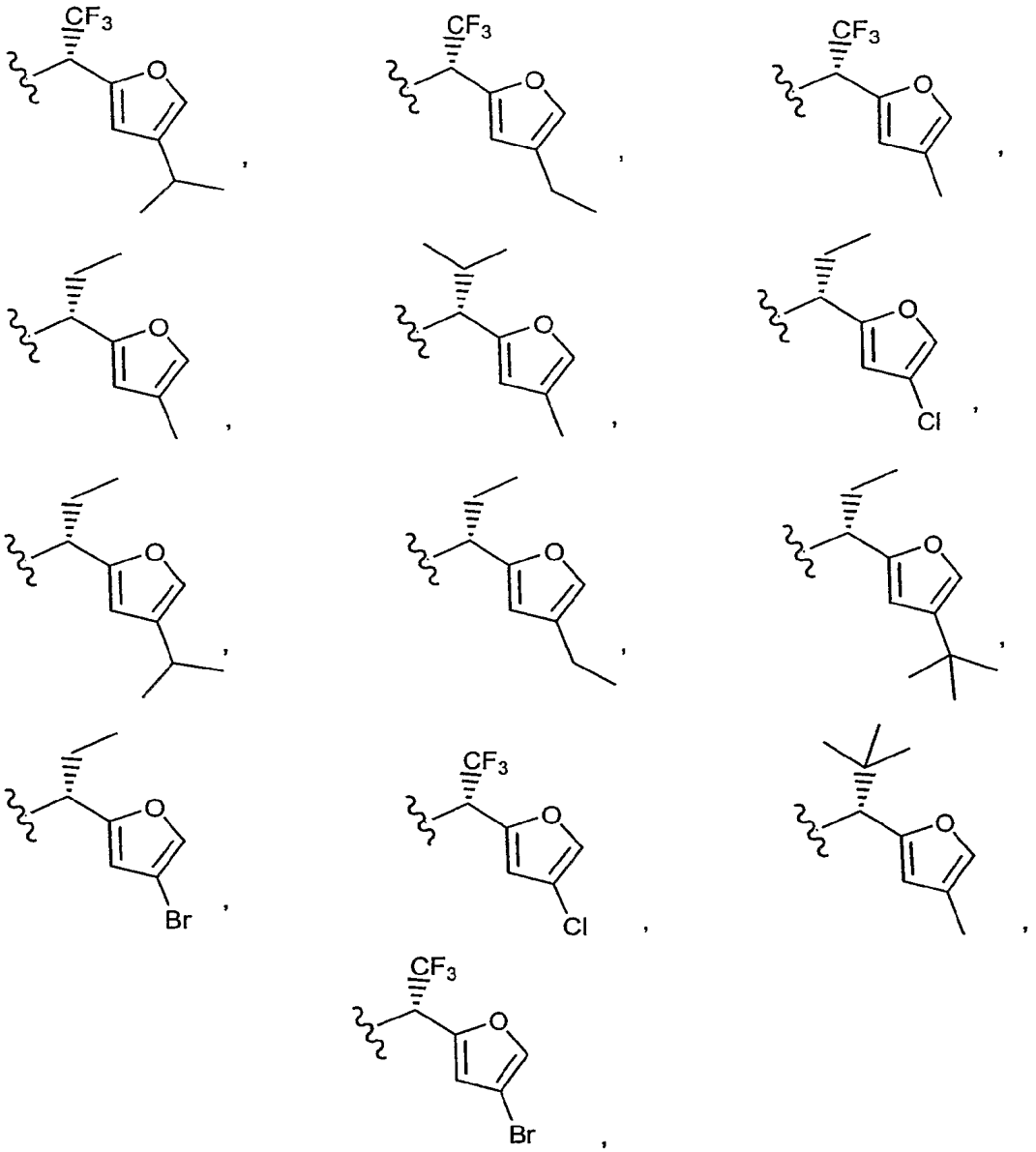
wherein the furan ring is substituted with at least one alkyl group.

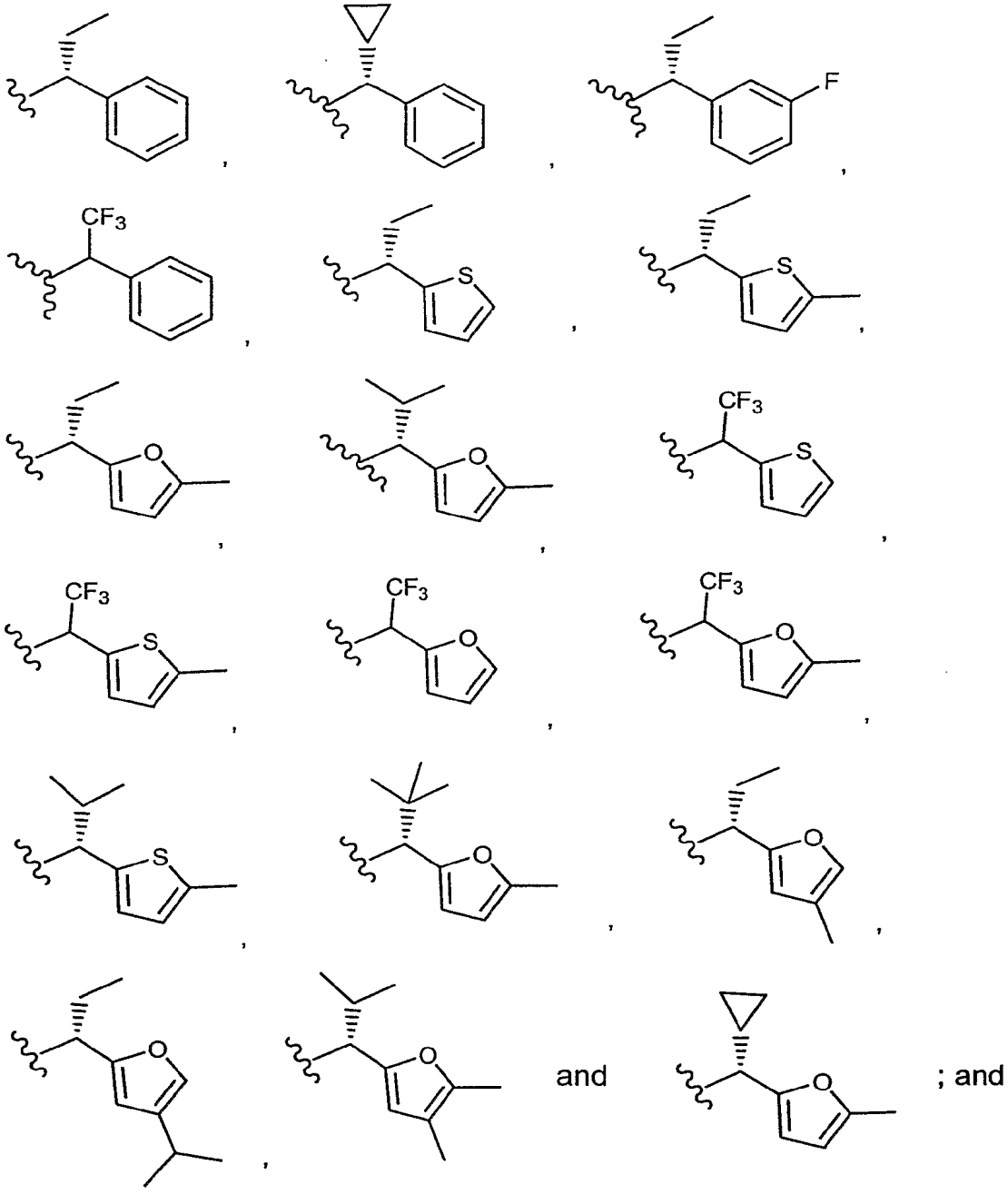
39. The use of Claim 38 wherein R^7 and R^8 are independently selected from the group consisting of: H and alkyl.

40. The use of Claim 39 wherein R^7 is H, and R^8 is alkyl.

41. The use of Claim 16 wherein

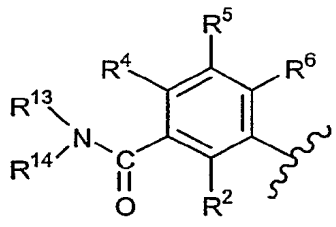
(1) A is selected from the group consisting of:





and ; and

(2) B is:



wherein:

R^2 is –OH;

R^4 is selected form the group consisting of: H, $-CH_3$ and $-CF_3$;

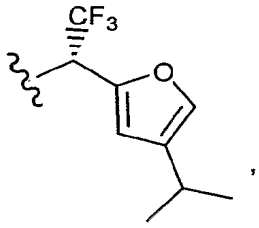
R^5 is selected from the group consisting of: H and cyano;

R^6 is selected from the group consisting of: H, $-CH_3$ and $-CF_3$;

R^{13} and R^{14} are methyl.

42. The use of Claim 16 wherein

(1) A is selected from the group consisting of:



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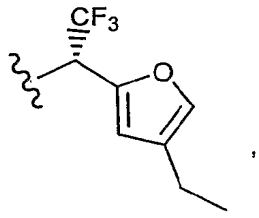

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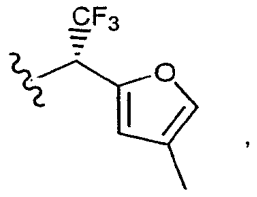

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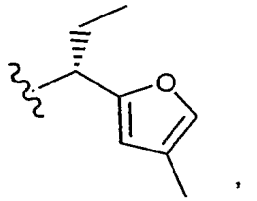

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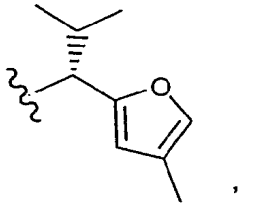

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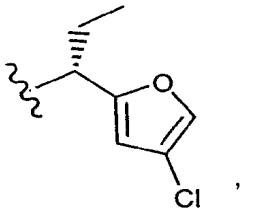

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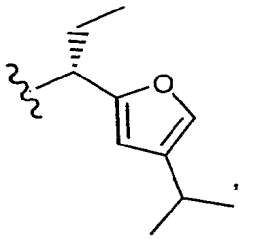

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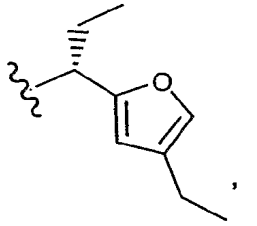

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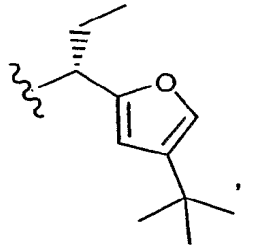

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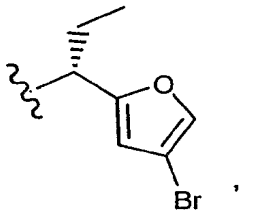

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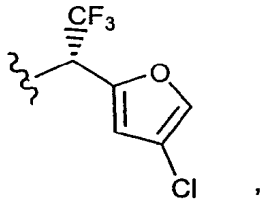

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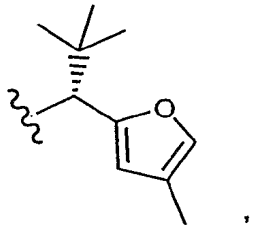

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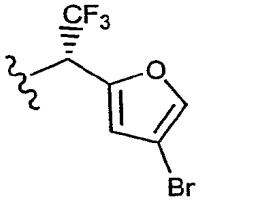

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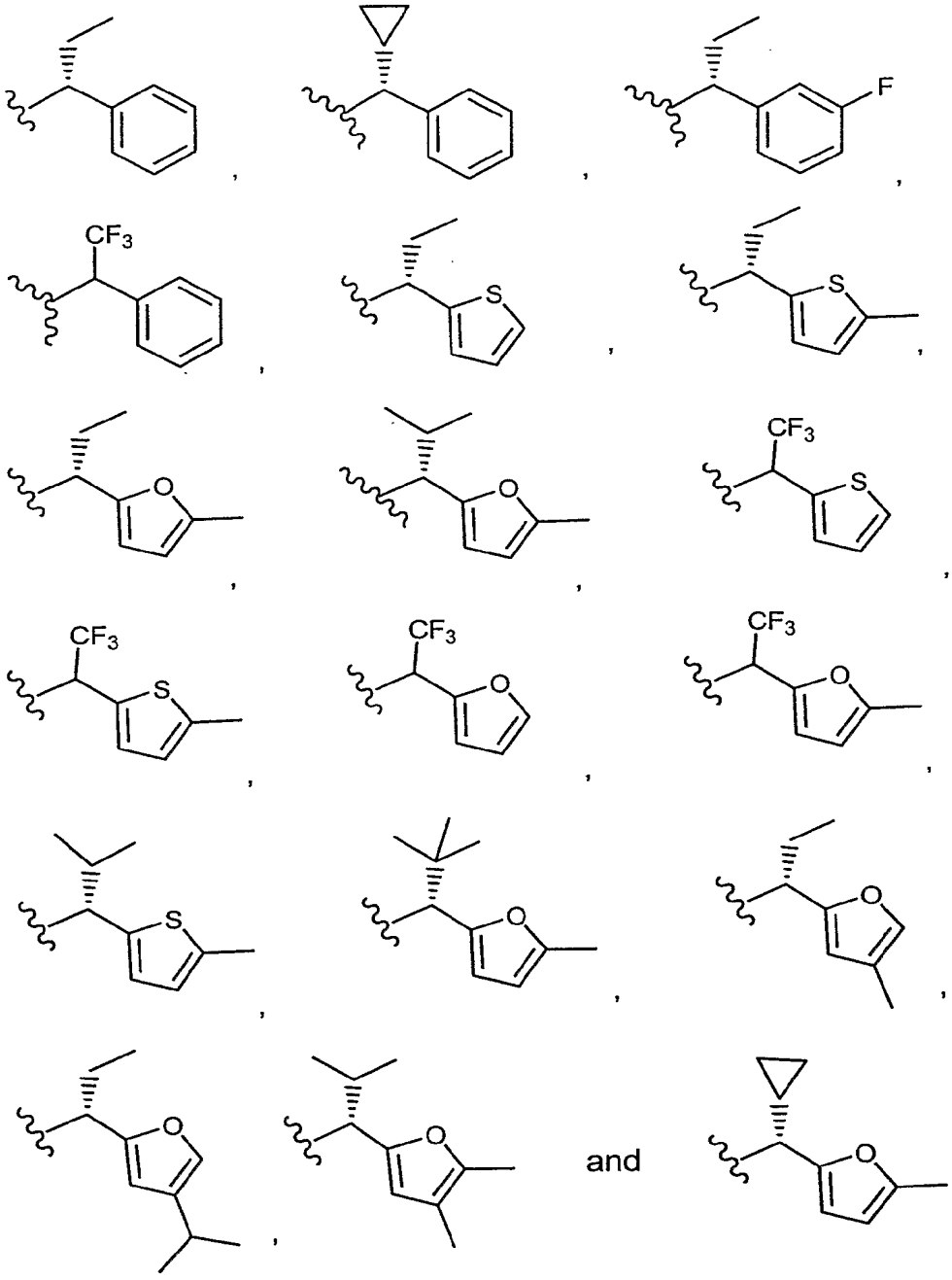
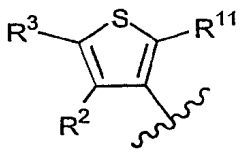


and ; and

(2) B is:



wherein:

R^2 is –OH;

R^3 is selected from the group consisting of: $-SO_2NR^{13}R^{14}$ and $-CONR^{13}R^{14}$;

R^{11} is H; and

each R^{13} and R^{14} are independently selected from the group consisting of: H, methyl, ethyl, isopropyl and t-butyl.

43. The use of Claim 42 wherein R^3 is $-SO_2NR^{13}R^{14}$.

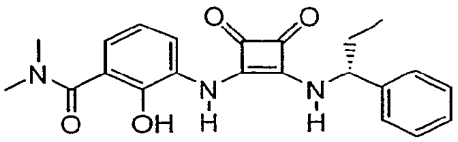
44. The use of Claim 43 wherein R^{13} and R^{14} are ethyl.

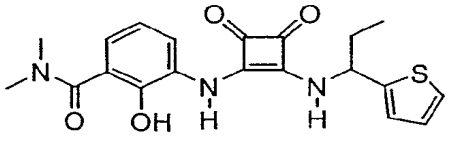
45. The use of Claim 16 wherein said compound is a calcium salt.

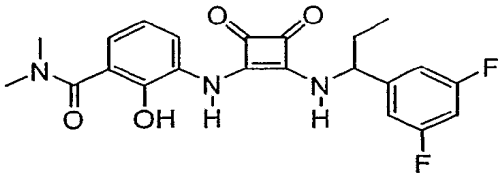
46. The use of Claim 16 wherein said compound is a sodium salt.

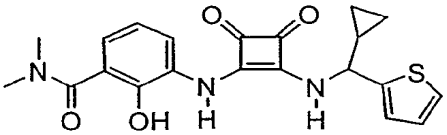
47. The use of Claim 16 wherein said disease is selected from the group consisting of: acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, and chronic neuropathic pain.

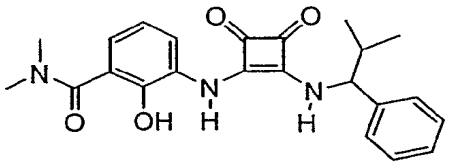
48. The use of Claim 16 wherein said compound is selected from the group consisting of:

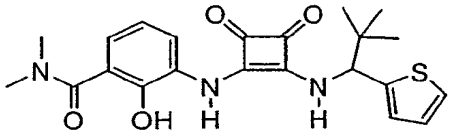


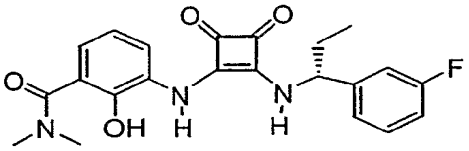


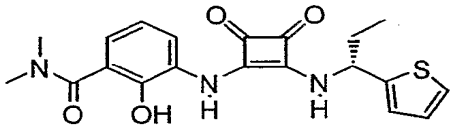


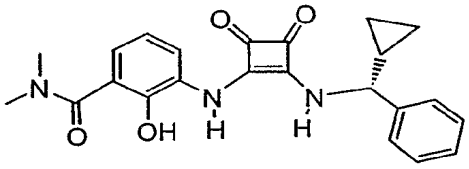


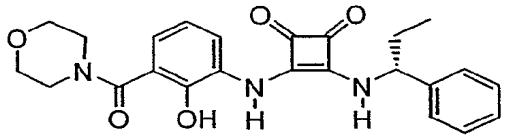


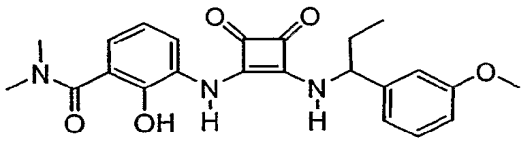


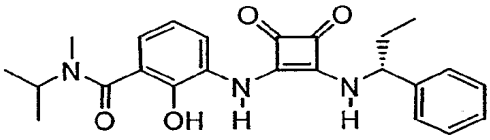


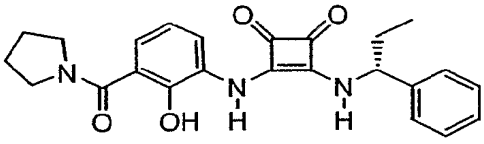


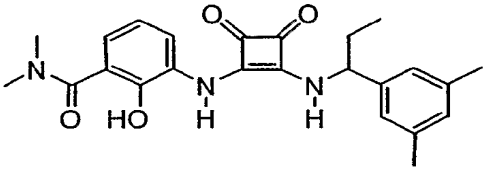


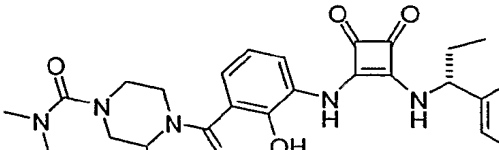


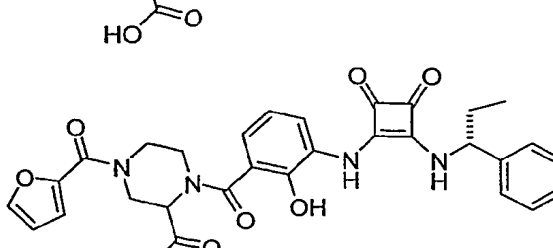


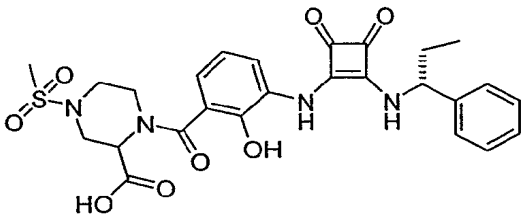


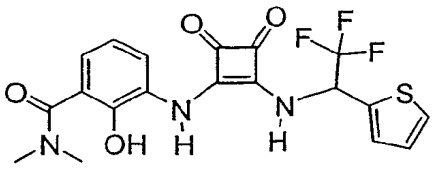


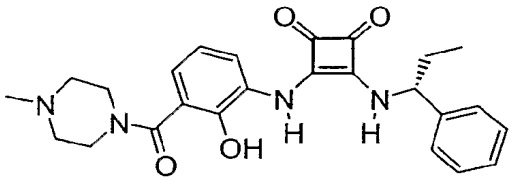


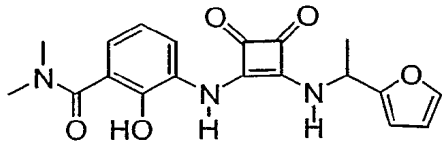


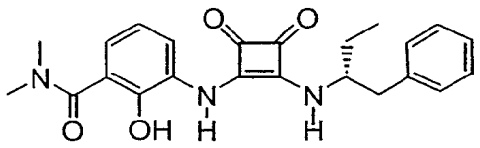


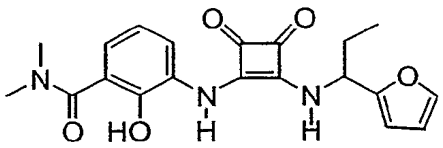


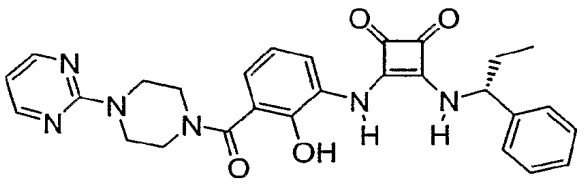


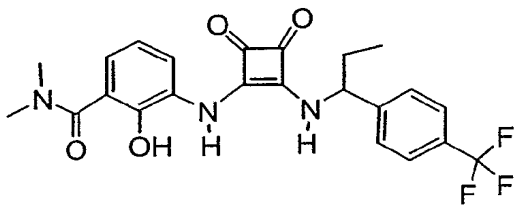


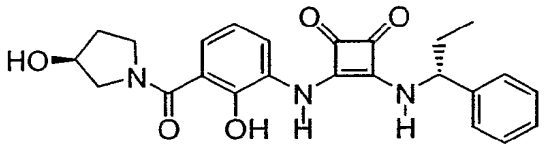


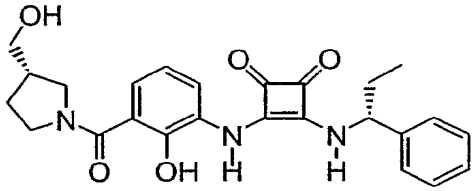


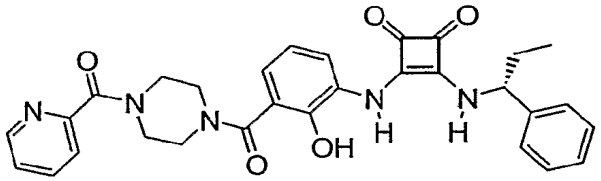


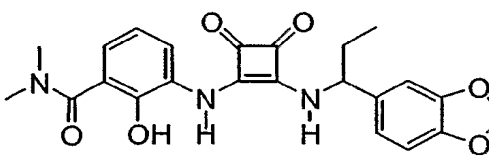


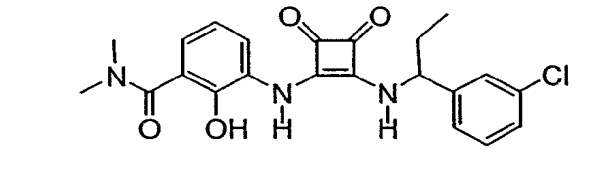


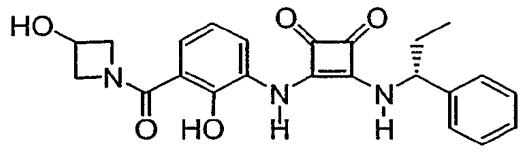


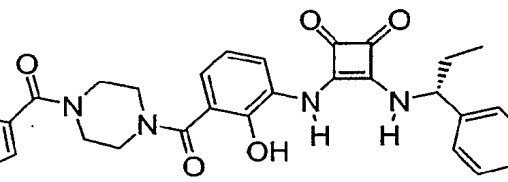


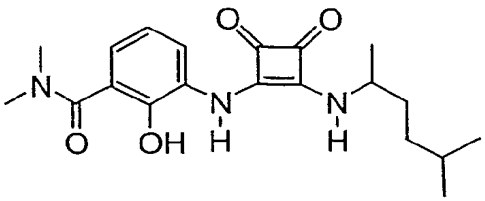


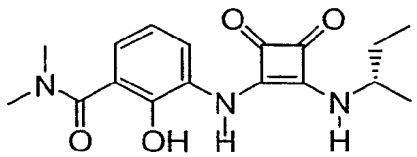


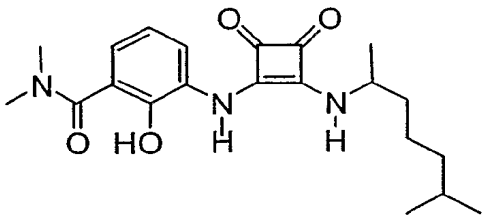


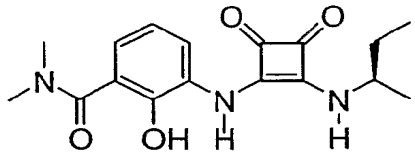


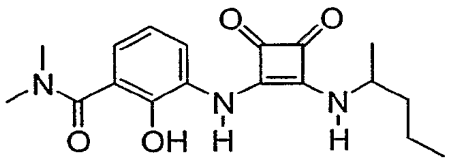


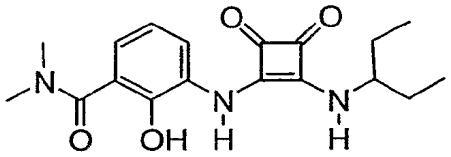


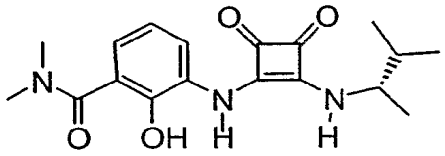


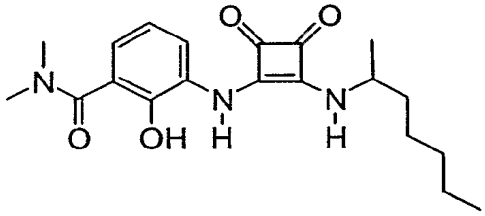


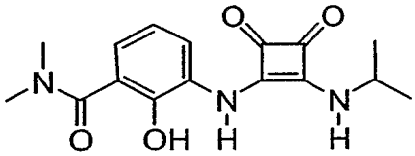


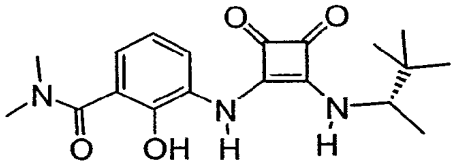


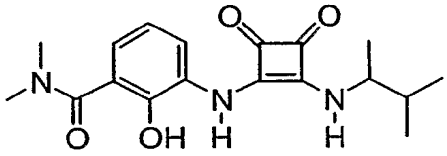


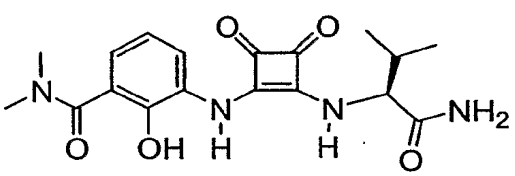


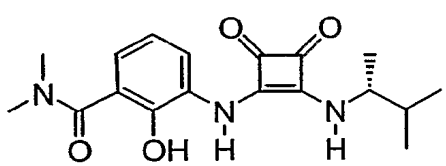


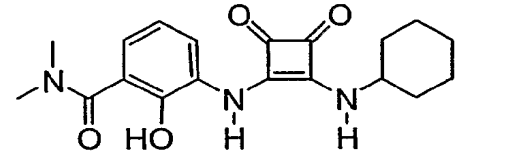


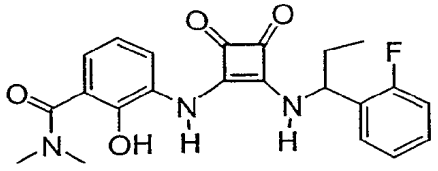


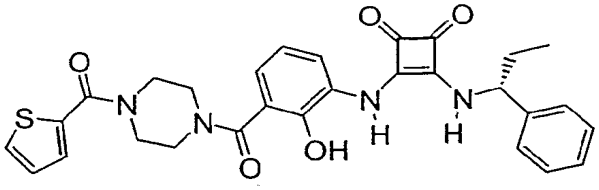


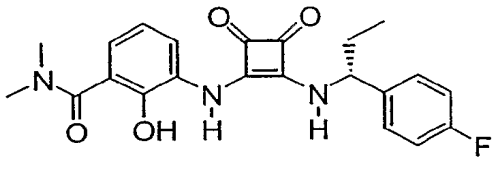


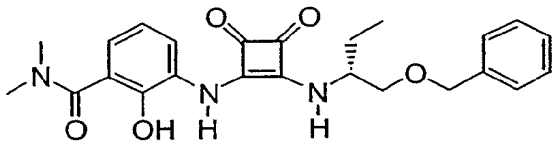


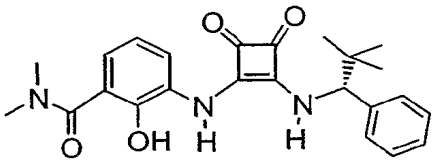


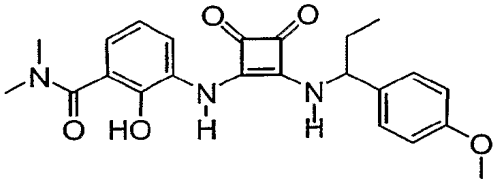


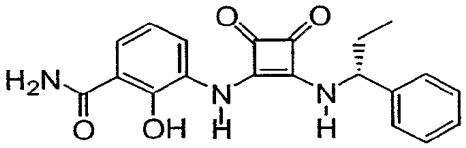


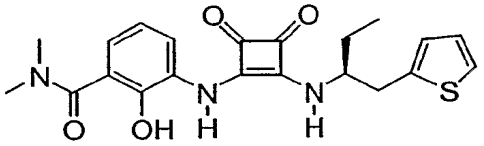


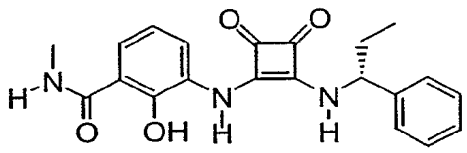


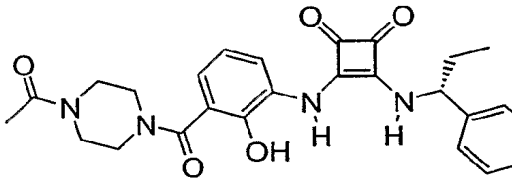


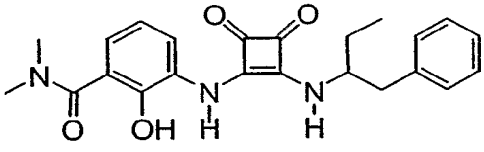


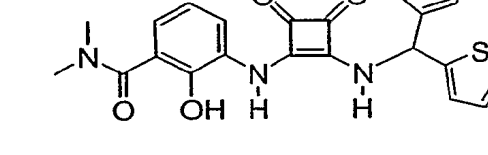


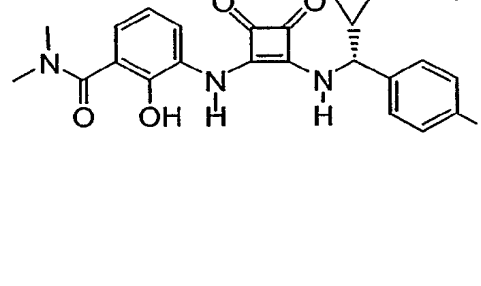


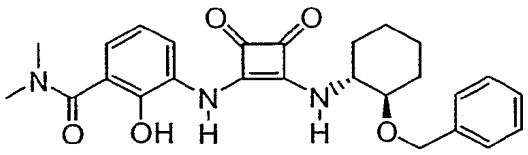


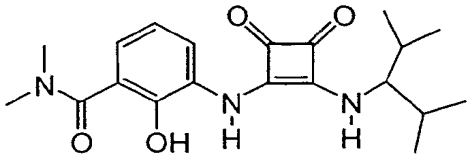


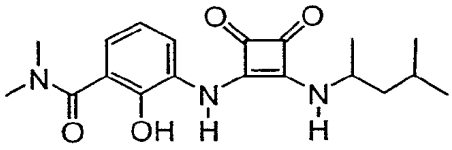


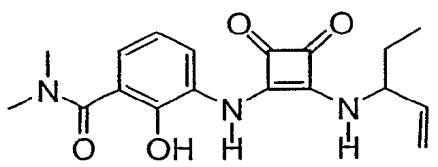


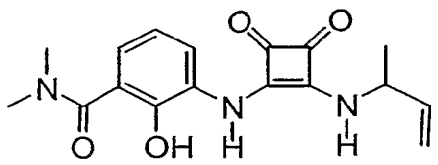


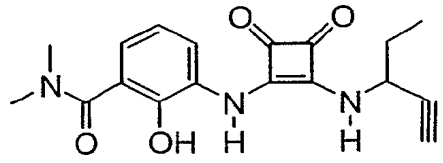


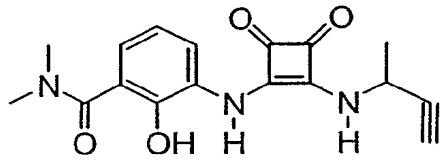


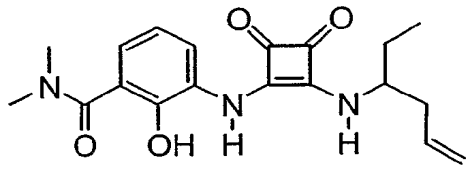


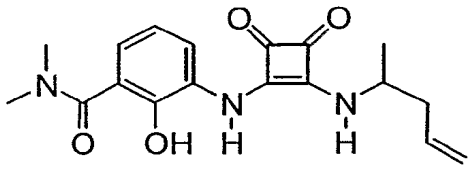


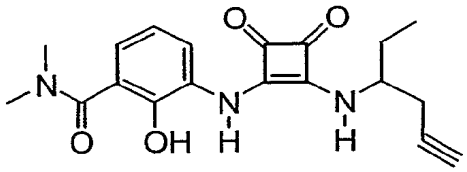


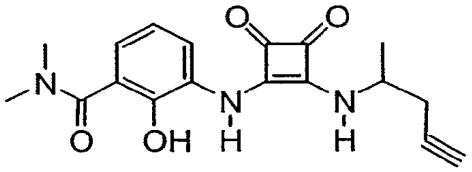


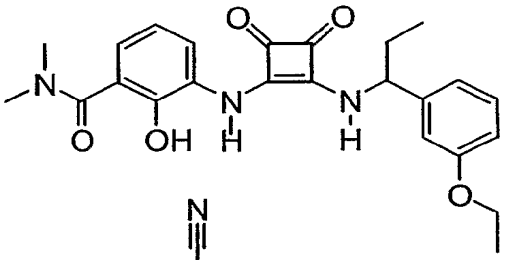


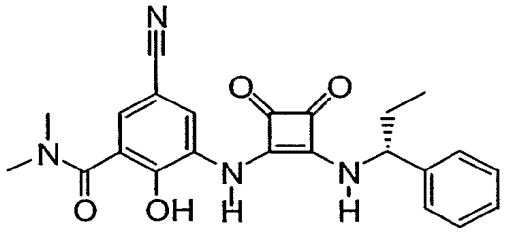


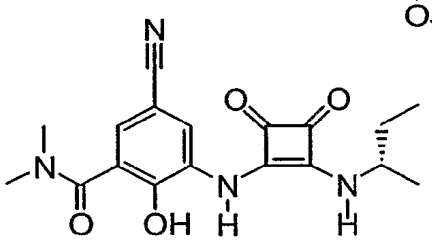


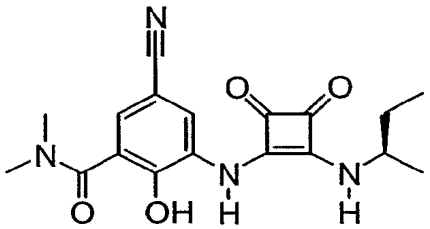


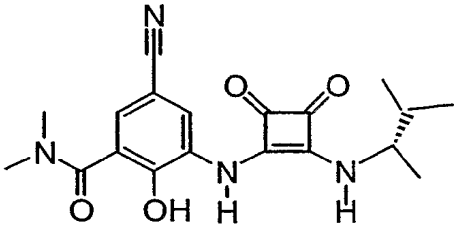


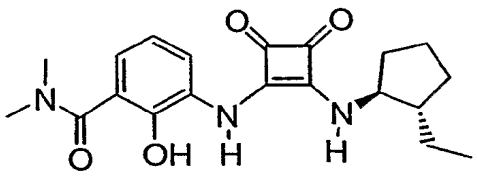


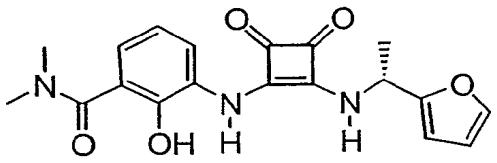


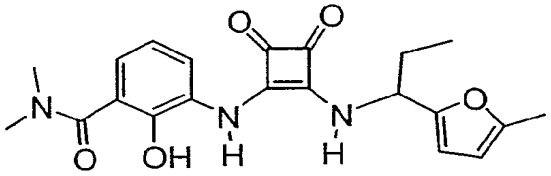


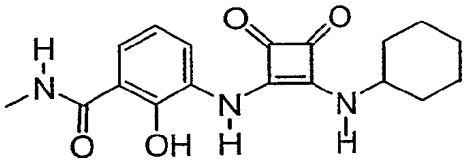


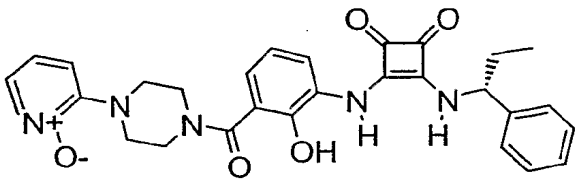


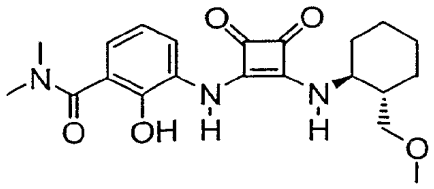


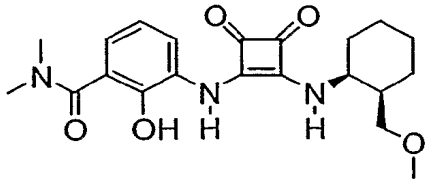


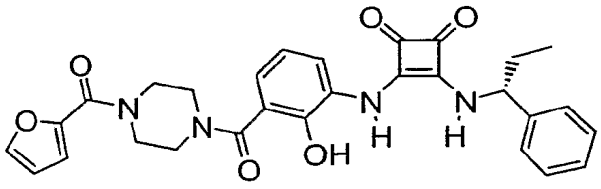


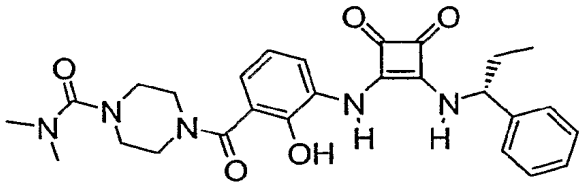


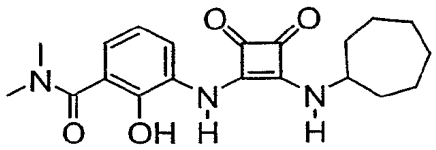


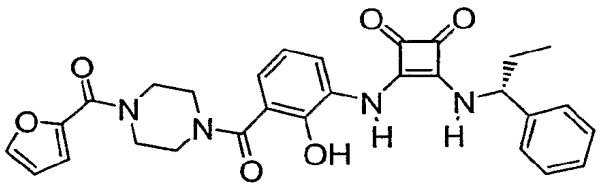


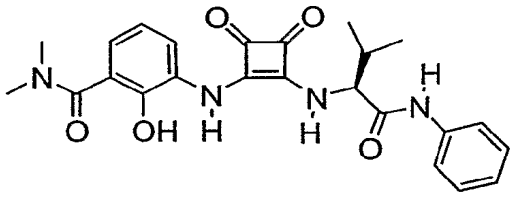


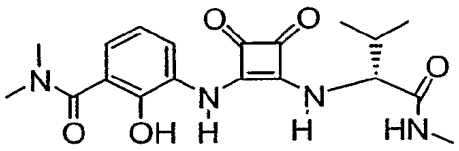


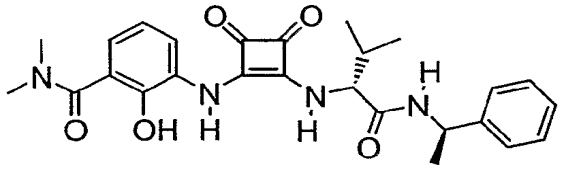


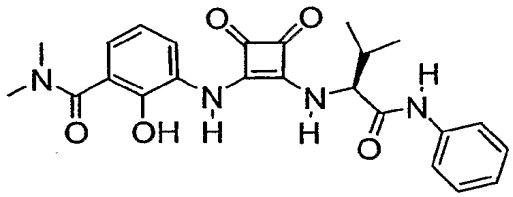


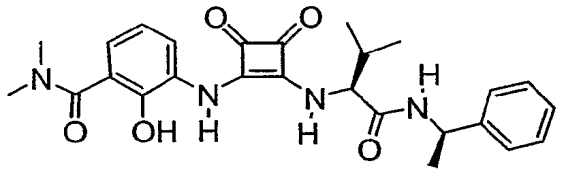


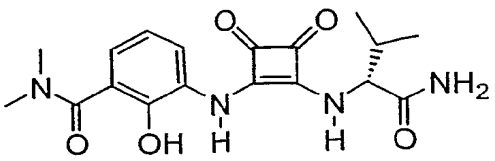


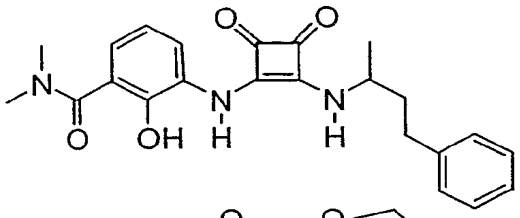


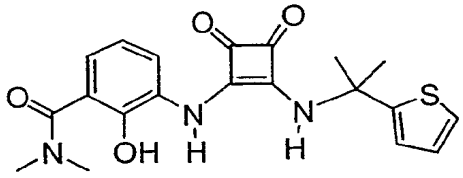


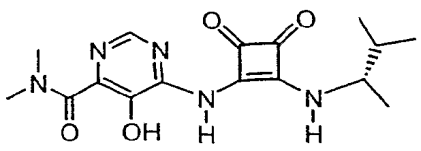


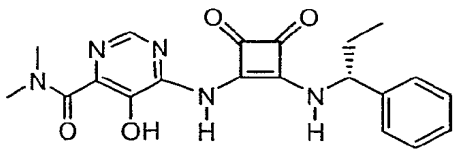


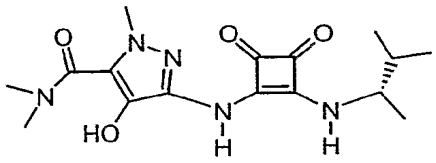


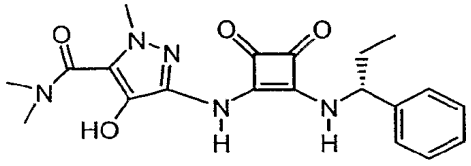


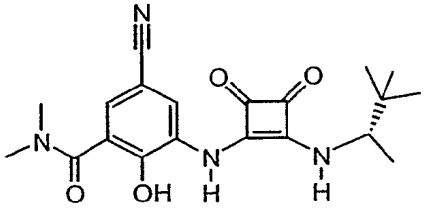


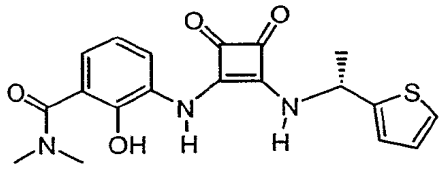


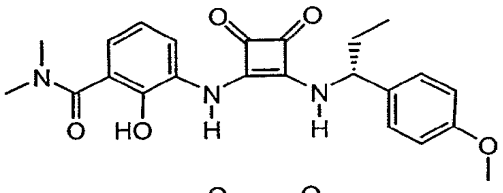


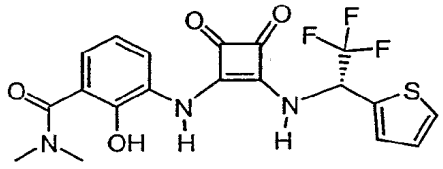


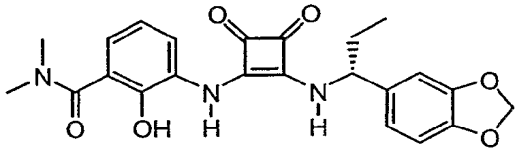


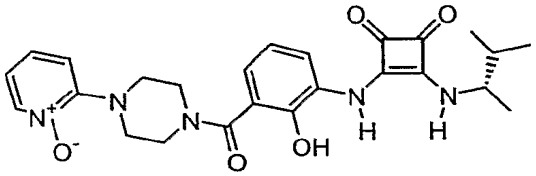


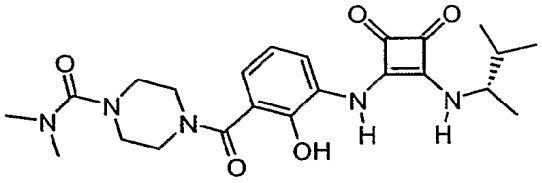


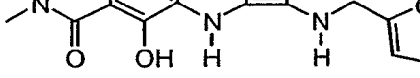


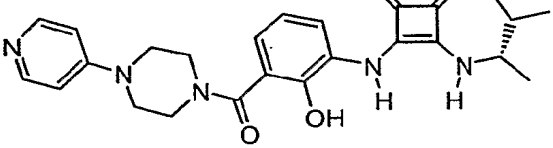


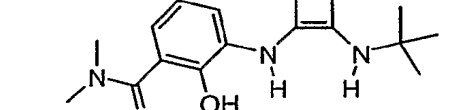


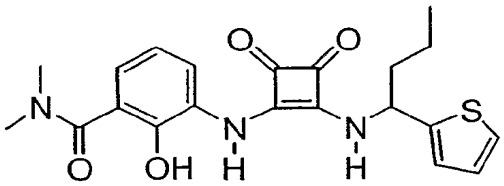


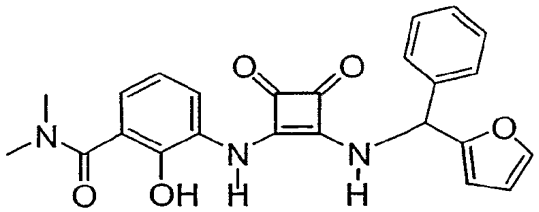


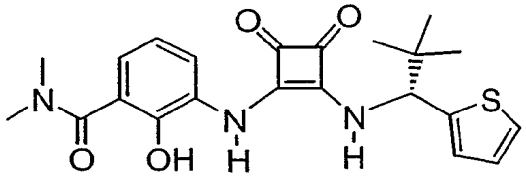


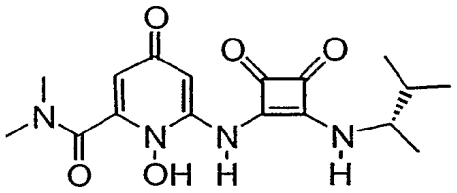


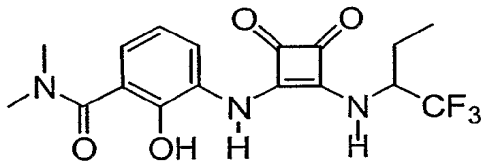


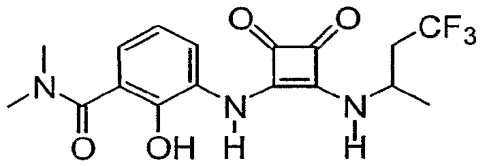


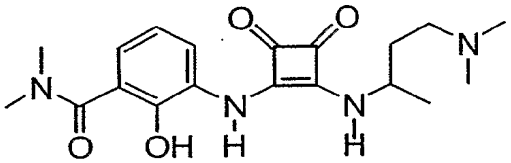


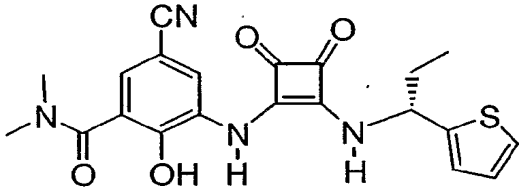


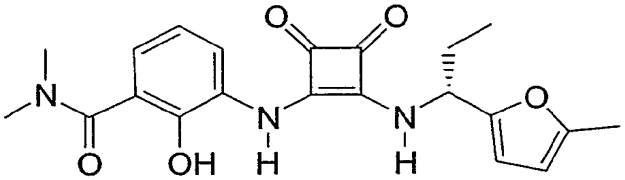


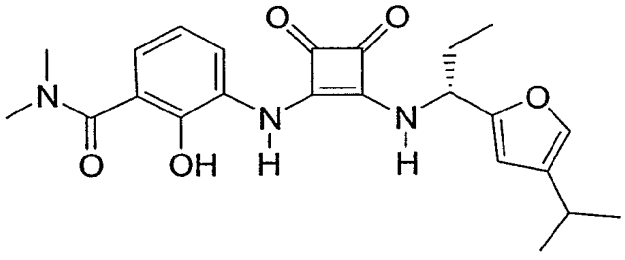


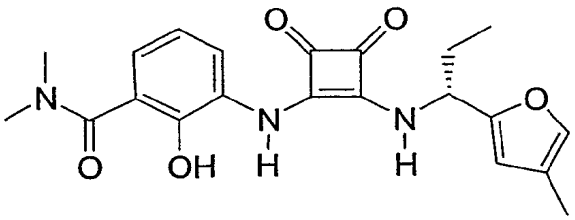


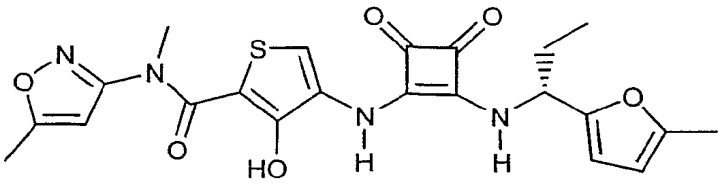


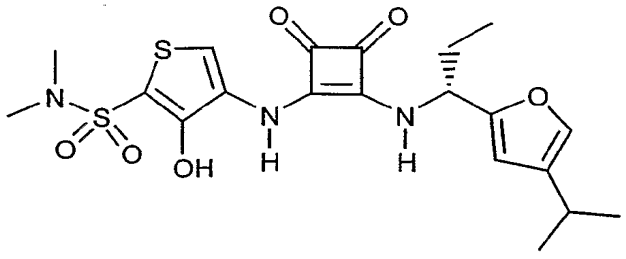




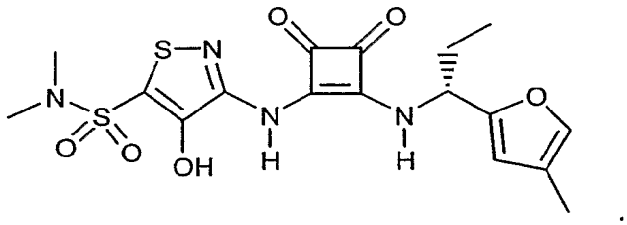






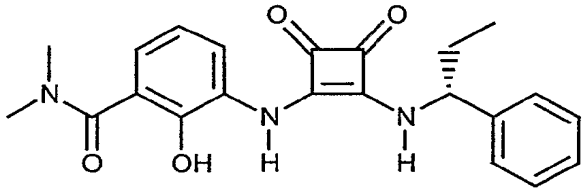


and



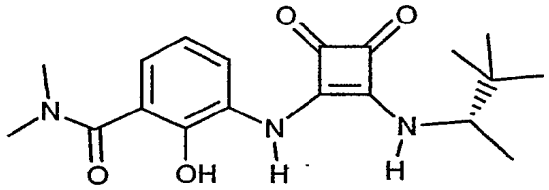
49. The use of Claim 48 wherein a calcium or sodium salt of the compounds is used.

50. The use of Claim 16 wherein said compound is:



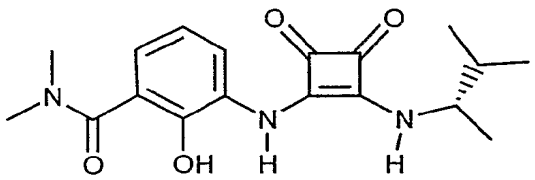
or a pharmaceutically acceptable salt or solvate thereof.

51. The use of Claim 16 wherein said compound is:



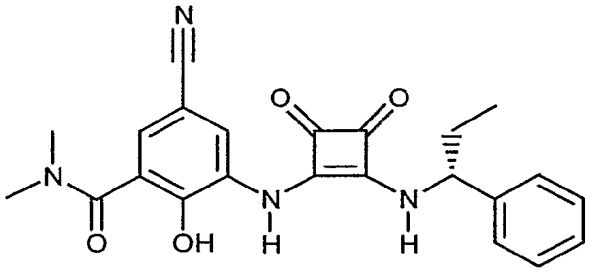
or a pharmaceutically acceptable salt or solvate thereof.

52. The use of Claim 16 wherein said compound is:



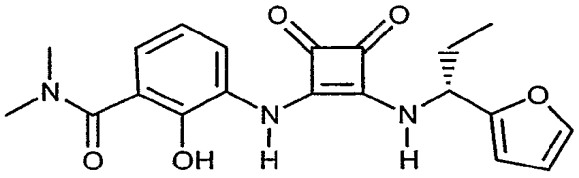
or a pharmaceutically acceptable salt or solvate thereof.

53. The use of Claim 16 wherein said compound is:



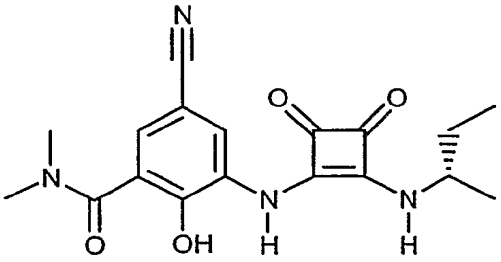
or a pharmaceutically acceptable salt or solvate thereof.

54. The use of Claim 16 wherein said compound is:



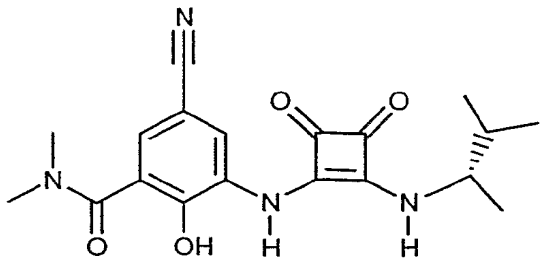
or a pharmaceutically acceptable salt or solvate thereof.

55. The use of Claim 16 wherein said compound is:



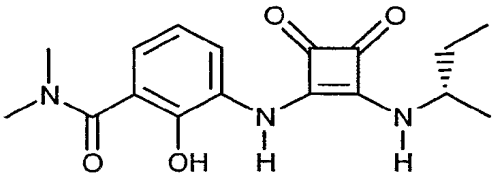
or a pharmaceutically acceptable salt or solvate thereof.

56. The use of Claim 16 wherein said compound is:



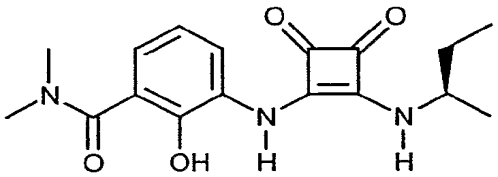
or a pharmaceutically acceptable salt or solvate thereof.

57. The use of Claim 16 wherein said compound is:



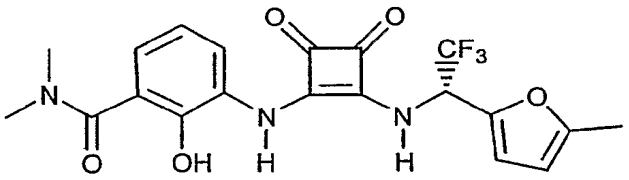
or a pharmaceutically acceptable salt or solvate thereof.

58. The use of Claim 16 wherein said compound is:



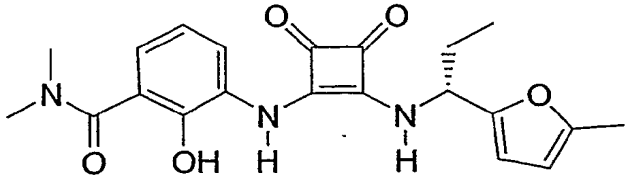
or a pharmaceutically acceptable salt or solvate thereof.

59. The use of Claim 16 wherein said compound is:



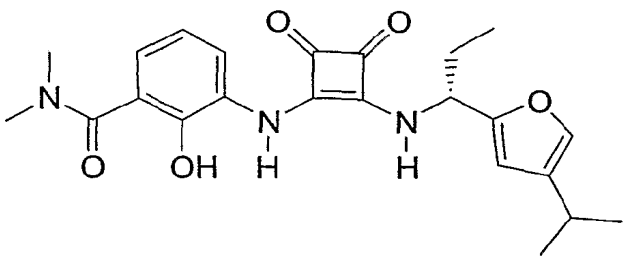
or a pharmaceutically acceptable salt or solvate thereof.

60. The use of Claim 16 wherein said compound is:



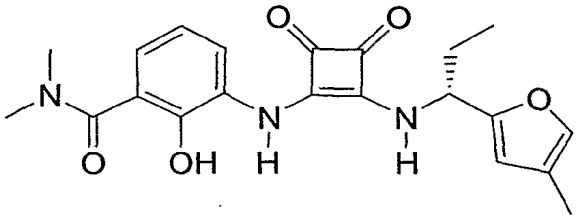
or a pharmaceutically acceptable salt or solvate thereof.

61. The use of Claim 16 wherein said compound is:



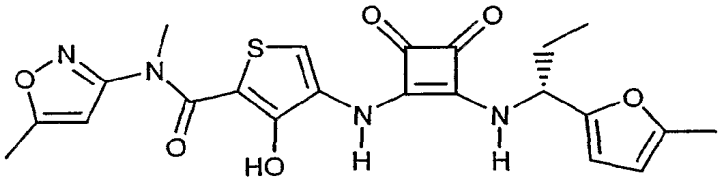
or a pharmaceutically acceptable salt or solvate thereof.

62. The use of Claim 16 wherein said compound is:



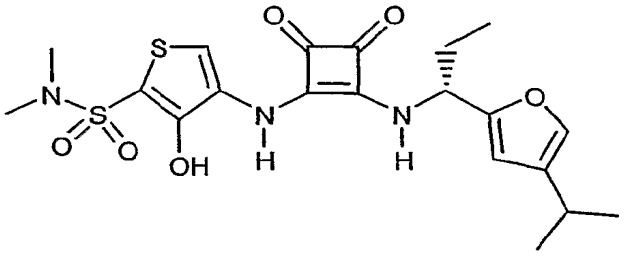
or a pharmaceutically acceptable salt or solvate thereof.

63. The use of Claim 16 wherein said compound is:



or a pharmaceutically acceptable salt or solvate thereof.

64. The use of Claim 16 wherein said compound is:



or a pharmaceutically acceptable salt or solvate thereof.

65. The use of anyone of Claims 50 to 64 wherein a calcium or sodium salt of said compound is used.

66. A use of at least one compound of any of Claims 1 to 13 for manufacturing a medicament for treating a chemokine-mediated disease, wherein the chemokine binds to a CXCR2 and/or CXCR1 receptor in a patient.

67. A use of at least one compound of any of Claims 1 to 13 for manufacturing a medicament for treating a chemokine-mediated disease, wherein the chemokine binds to a CXC receptor in a patient.

68. The use of Claim 66 wherein the chemokine mediated disease is selected from the group consisting of: chronic inflammation, acute inflammatory pain, chronic inflammatory pain, acute neuropathic pain, chronic neuropathic pain, psoriasis, atopic dermatitis, asthma, COPD, adult respiratory disease, arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, stroke, cardiac and renal reperfusion injury, glomerulonephritis, thrombosis, Alzheimer's disease, graft vs. host reaction, allograft rejections, malaria, acute respiratory distress syndrome, delayed type hypersensitivity reaction, atherosclerosis, cerebral and cardiac ischemia, osteoarthritis, multiple sclerosis, restinosis, angiogenesis, osteoporosis, gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, Kaposi's sarcoma associated virus, meningitis, cystic fibrosis, pre-term labor, cough, pruritis, multi-organ dysfunction, trauma, strains, sprains, contusions, psoriatic arthritis, herpes, encephalitis, CNS vasculitis, traumatic brain injury, CNS tumors, subarachnoid hemorrhage, post surgical trauma, interstitial pneumonitis, hypersensitivity, crystal induced arthritis, acute and chronic pancreatitis, acute alcoholic hepatitis, necrotizing enterocolitis, chronic sinusitis, angiogenic ocular disease, ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization, polymyositis, vasculitis, acne, gastric and duodenal ulcers, celiac disease, esophagitis, glossitis, airflow obstruction, airway hyperresponsiveness, bronchiectasis, bronchiolitis, bronchiolitis obliterans, chronic bronchitis, cor pulmonae, cough, dyspnea, emphysema, hypercapnea, hyperinflation,

hypoxemia, hyperoxia-induced inflammations, hypoxia, surgical lung volume reduction, pulmonary fibrosis, pulmonary hypertension, right ventricular hypertrophy, peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD), granulocytic ehrlichiosis, sarcoidosis, small airway disease, ventilation-perfusion mismatching, wheeze, colds, gout, alcoholic liver disease, lupus, burn therapy, periodontitis, transplant reperfusion injury and early transplantation rejection, acute inflammation, and rheumatoid arthritis.

69. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating cancer.

70. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating cancer, the treatment comprising administering said medicament in combination with the administration of at least one anticancer agent.

71. The use of Claim 70 wherein said anticancer agent is selected from the group consisting of: alkylating agents, antimetabolites, natural products and their derivatives, hormones, anti-hormones, anti-angiogenic agents and steroids, and synthetics.

72. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for inhibiting angiogenesis.

73. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for inhibiting angiogenesis, the inhibition comprising administering said medicament in combination with the administration of at least one anti-angiogenesis compound.

74. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating a disease selected from the group consisting of: gingivitis, respiratory viruses, herpes viruses, hepatitis viruses, HIV, kaposi's sarcoma associated virus and atherosclerosis.

75. The use of Claim 66 wherein the chemokine mediated disease is an angiogenic ocular disease.

76. The use of Claim 75 wherein said angiogenic ocular disease is selected from the group consisting of: ocular inflammation, retinopathy of prematurity, diabetic retinopathy, macular degeneration with the wet type preferred and corneal neovascularization.

77. The use of Claim 69 wherein the cancer treated is melanoma, gastric carcinoma, or non-small cell lung carcinoma.

78. The use of Claim 70 wherein the cancer treated is melanoma, gastric carcinoma, or non-small cell lung carcinoma.

79. The use of Claim 71, wherein the cancer treated is melanoma, gastric carcinoma, or non-small cell lung carcinoma.

80. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating acute inflammatory pain.

81. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating chronic inflammatory pain.

82. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating acute neuropathic pain.

83. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating chronic neuropathic pain.

84. A use of at least one compound of any of Claims 1 to 13 for the manufacture of a medicament for treating COPD.

85. The use of Claim 16 wherein said disease is acute inflammatory pain.

86. The use of Claim 16 wherein said disease is chronic inflammatory pain.

87. The use of Claim 16 wherein said disease acute neuropathic pain.

88. The use of Claim 16 wherein said disease is chronic neuropathic pain.

89. The use of Claim 16 wherein said disease is acute inflammation.

90. The use of Claim 16 wherein said disease is rheumatoid arthritis.

91. The use of any of Claims 48 to 64 wherein said disease is acute inflammation.

92. The use of any of Claims 48 to 64 wherein said disease is rheumatoid arthritis.

93. The use of Claim 91 wherein the medicament is manufactured from a calcium or sodium salt of the compound.

94. The use of Claim 92 wherein the medicament is manufactured from a calcium or sodium salt of the compound.

95. A compound selected from the group consisting of the final compounds of Examples 2006, 2010, 2015, 2029, 2034, 2035, 2038, 2039, 2047, 2050, 2074, 2079 and 2087.

96. The compound of Claim 95 wherein the compound is a calcium or sodium salt.

97. A pharmaceutical composition comprising an effective amount of at least one compound of any of Claims 95 to 96, and a pharmaceutically acceptable carrier.

98. A use of at least one compound of any of Claims 1 to 13, 95 and 96 for the manufacture of a medicament for the treatment of acute inflammation.

99. A use of at least one compound of any of Claims 1 to 13, 95 and 96 for the manufacture of a medicament for the treatment of rheumatoid arthritis.

100. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of COPD.

101. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of acute inflammatory pain.

102. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of chronic inflammatory pain.

103. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of acute neuropathic pain.

104. A use of at least one compound of any of Claims 95 to 96 for the manufacture of a medicament for the treatment of chronic neuropathic pain.

106. A use of at least one compound of any of Claims 1 to 13, 95 and 96 for the manufacture of a medicament for the treatment of chronic inflammation.

107. A use of at least one compound of any of Claims 16 and 48 to 64 for the manufacture of a medicament for the treatment of chronic inflammation.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/23785

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C237/36 C07C237/44 C07C311/39 C07D207/323 C07D217/24
C07D307/52 C07D307/68 C07D307/81 C07D307/82 C07D307/83
C07D317/46 C07D319/18 C07D333/20 C07D405/12 C07D409/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 083624 A (SCHERING CORP ;PHARMACOPEIA INC (US)) 24 October 2002 (2002-10-24) cited in the application page 61; claims; example 360.63	1-107
Y	WO 01 92202 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US); BI GUANGPING) 6 December 2001 (2001-12-06) page 16, line 2 -page 17, line 18; claims	1-107
Y	WO 01 68569 A (SMITHKLINE BEECHAM CORP ;WIDDOWSON KATHERINE L (US); JIN QI (US)) 20 September 2001 (2001-09-20) page 19, line 20 -page 21, line 6; claims 1,14-16	1-107

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2003	17/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hanisch, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/23785

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D409/14 C07D413/12 C07D413/14 A61K31/341 A61K31/36
A61K31/381 A61K31/40 A61K31/4025 A61K31/42 A61K31/472
A61K31/496 A61K31/506 A61K31/5377 A61P29/00 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 35855 A (AMERICAN HOME PROD) 22 June 2000 (2000-06-22) page 47, line 3 - line 8; claims 1,37-39	1-107
E	WO 2003 080053 A (SCHERING CORPORATION, USA) 2 October 2003 (2003-10-02) page 148 -page 155; claims	9-107

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hanisch, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/23785

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2003	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hanisch, I

INTERNATIONAL SEARCH REPORT

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